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(54) Title: NOVEL TRICYCLIC SPIRODERIVATIVES AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

(57) Abstract: The invention provides compounds of formula (I) wherein m, R¹, n, R², q, p, X, Y, R³, R⁴, t and, R⁵ are as defined in the specification, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

Novel tricyclic spiroderivatives as modulators of chemokine receptor activity

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy. In particular, the 5 invention relates to novel spirocyclic compounds, their preparation and use.

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted 10 molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

15

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2). The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and 20 MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1 α and 1 β (MIP-1 α and MIP-1 β).

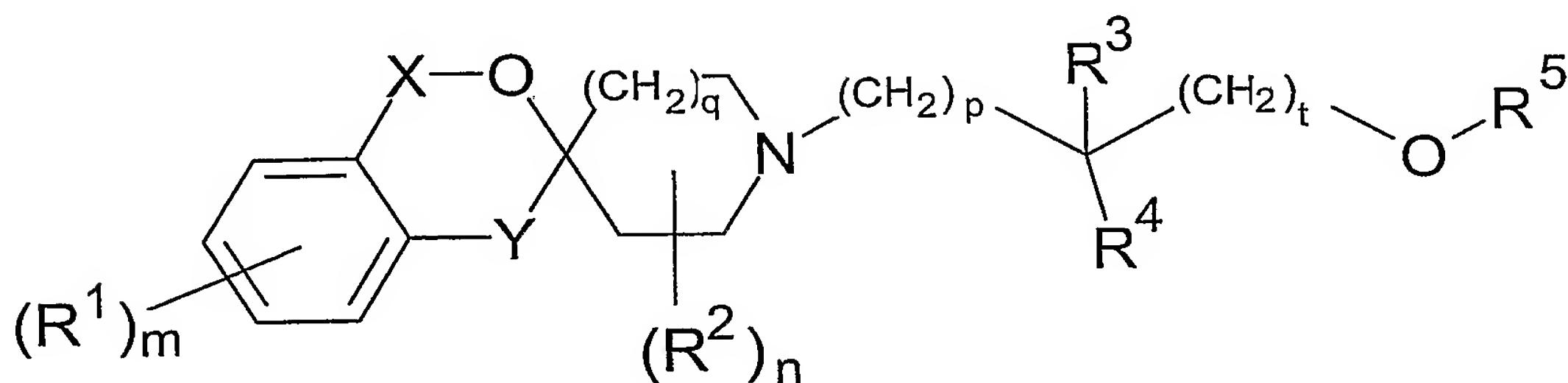
Studies have demonstrated that the actions of the chemokines are mediated by subfamilies 25 of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

30 Spiro(dihydrobenzofuran)piperidines and pyrrolidines having activity as analgesics and tranquillising agents are described in US 4,166,119. Spiro(2,3-dihydrobenzofuran-2,4-

piperid-1-yl) derivatives of interest inter alia as antipsychotic and cerebral ischaemic agents are described in EP 0 351 282 B.

In accordance with the present invention, there is provided a compound of formula (I)

5



(I)

10 wherein

m is 0, 1, 2, 3 or 4;

each R^1 independently represents halogen, cyano, hydroxyl, C_1 - C_6 alkyl,

C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylsulphonyl or sulphonamido ($-SO_2NH_2$);

15 X represents a bond or $-CH_2-$ and Y represents a bond or $-CH_2-$, provided that X and Y do not both simultaneously represent a bond or $-CH_2-$;

n is 0, 1 or 2;

each R^2 independently represents halogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl;

q is 0 or 1;

20 p is 0, 1 or 2;

R^3 represents a group selected from halogen, NR^6R^7 , carboxyl or C_1 - C_6 alkyl wherein said C_1 - C_6 alkyl group is optionally substituted by one or more halogen, amino, hydroxyl, C_1 - C_6 alkoxy, N -(C_1 - C_6 alkyl)amino, N,N -di- $(C_1$ - C_6 alkyl)amino, carboxy or carbamoyl;

R^4 represents hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl or halogen;

25 t is 0, 1 or 2, provided that p and t are not both 0;

R^5 represents a saturated or unsaturated 5- to 10-membered ring system which ring system may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by one or more substituents independently selected from halogen, cyano, oxo, nitro, hydroxyl, carboxyl, $-C(O)H$, $-NR^8R^9$,
5 $-C(O)NR^{10}R^{11}$, $-NHC(O)R^{12}$, $-NHSO_2R^{13}$, $-SO_2NR^{14}R^{15}$, $-NHC(O)NR^{16}R^{17}$, a group selected from C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 alkylsulphonyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylcarbonyl, phenylcarbonyl, C_3 - C_6 cycloalkyl, phenyl and a saturated or unsaturated 5- to 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each 10 group being optionally substituted by one or more substituents independently selected from halogen, cyano, hydroxyl, carboxyl, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 alkoxy and C_1 - C_6 alkoxy carbonyl;

R^6 and R^7 each independently represent hydrogen or a group selected from C_1 - C_6 alkyl and
15 C_1 - C_6 alkylcarbonyl, each of which may be optionally substituted by one or more substituents selected from halogen, amino, hydroxyl, C_1 - C_6 alkoxy, N -(C_1 - C_6 alkyl)amino, N,N -di-(C_1 - C_6 alkyl)amino, carboxy, carbamoyl or C_1 - C_6 alkoxy carbonyl, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 4- to 7-membered 20 saturated heterocyclic ring which may be optionally substituted by one or more substituent selected from halogen, amino, hydroxyl, C_1 - C_6 alkoxy, N -(C_1 - C_6 alkyl)amino, N,N -di-(C_1 - C_6 alkyl)amino, carboxy, carbamoyl or C_1 - C_6 alkoxy carbonyl;

R^8 , R^9 , R^{10} , R^{11} each independently represent hydrogen or a group selected from C_1 - C_6 alkyl or C_3 - C_6 cycloalkyl, each group being optionally substituted by one or more substituents independently selected from halogen, amino, hydroxyl, C_1 - C_6 alkoxy, N -(C_1 - C_6 alkyl)amino, N,N -di-(C_1 - C_6 alkyl)amino, carboxy or carbamoyl; or R^{10} and R^{11} , together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring which may be optionally substituted with at least one substituent selected from halogen, amino, hydroxyl, C_1 - C_6 alkoxy, N -(C_1 - C_6 alkyl)amino, N,N -di-(C_1 - C_6 alkyl)amino, carboxy or carbamoyl;
30

R¹² represents hydrogen or a group selected from C₁-C₆ alkyl or C₃-C₆ cycloalkyl, each group being optionally substituted by one or more substituents independently selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl;

5

R¹³ represents a group selected from C₁-C₆ alkyl or C₃-C₆ cycloalkyl, each group being optionally substituted by one or more substituents independently selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl;

10

R¹⁴, R¹⁵, R¹⁶ and R¹⁷ each independently represent hydrogen or a group selected from C₁-C₆ alkyl or C₃-C₆ cycloalkyl, each group being optionally substituted by one or more substituents independently selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl; or R¹⁴ and R¹⁵, or R¹⁶ and R¹⁷, together with the nitrogen atom to which they are attached each independently form a 4- to 7-membered saturated heterocyclic ring which may be optionally substituted with at least one substituent selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl;

15

20 or a pharmaceutically acceptable salt or solvate thereof.

Unless otherwise indicated, the term 'alkyl' when used alone or in combination, refers to a straight chain or branched chain alkyl moiety. A C₁-C₆ alkyl group has from one to six carbon atoms including methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl, n-hexyl and the like. References to 'C₁-C₄ alkyl' will be understood accordingly to mean a straight or branched chain alkyl moiety having from 1 to 4 carbon atoms. References to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only.

30

Analogously, the terms ‘C₁-C₆ alkoxy’ and ‘C₁-C₄ alkoxy’, when used alone or in combination, will be understood to refer to straight or branched chain groups having from one to six or from one to four carbon atoms respectively and includes such groups as methoxy, ethoxy, propoxy, isopropoxy, n- butoxy, isobutoxy, n-pentoxy or n-hexoxy.

5

A ‘C₂-C₆ alkenyl’ group refers to a straight or branched chain group having from two to six carbon atoms such as vinyl, isopropenyl, allyl and but-2-enyl. A C₂-C₆ alkynyl group is suitably ethynyl, 1-propynyl and propyn-2-yl.

10 The term ‘cycloalkyl’, when used alone or in combination, refers to a saturated alicyclic moiety having from three to six carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. A C₃-C₆ cycloalkylmethyl group is suitably cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl or cyclohexylmethyl.

15 As used herein, the term ‘halogen’ includes fluorine, chlorine, bromine and iodine.

A haloalkyl substituent group will comprise at least one halogen atom, for example one, two, three, four or five halogen atoms. Suitable values include trifluoromethyl or pentafluoroethyl.

20

A C₁-C₆ alkysulphonyl group is suitably a methylsulphonyl, ethylsulphonyl, n-propylsulphonyl, isopropylsulphonyl, n-butylsulphonyl, isobutylsulphonyl, tert-butylsulphonyl, n-pentylsulphonyl or n-hexylsulphonyl.

25 Suitable values for a C₁-C₆ alkylthio group include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, tert-butylthio, n-pentylthio or n-hexylthio.

Examples of *N*-(C₁-C₆ alkyl)amino groups include methylamino and ethylamino.

Examples of *N,N*-di-(C₁-C₆ alkyl)amino groups include di-N-methylamino, di-N-ethylamino and N-ethyl-N-methylamino.

A C₁-C₆ alkoxy carbonyl group is suitably methoxycarbonyl, ethoxycarbonyl, n- and t-butoxycarbonyl.

Examples of C₁-C₆ alkyl carbonyl groups include methyl carbonyl, ethyl carbonyl,

5 n-propyl carbonyl, isopropyl carbonyl, n-butyl carbonyl, isobutyl carbonyl, tert-butyl carbonyl, n-pentyl carbonyl or n-hexyl carbonyl

‘Optionally substituted’ is used herein to indicate optional substitution by the group or groups specified at any suitable available position.

10

In the ring substituted by R², R² may be attached to any suitable ring carbon atom including the carbon atom of (CH₂)_q

15 A ‘heteroatom’ is a nitrogen, sulphur or oxygen atom. Where rings include nitrogen atoms, these may be substituted as necessary to fulfil the bonding requirements of nitrogen or they may be linked to the rest of the structure by way of the nitrogen atom. Nitrogen atoms may also be in the form of N-oxides. Sulphur atoms may be in the form of S, S(O) or SO₂.

20 A ‘saturated or unsaturated 5- to 10-membered ring system which ring system may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur’ will be understood to refer to a monocyclic or polycyclic (for example, bicyclic), alicyclic or aromatic ring, carbocyclic or heterocyclic ring system containing from 5 to 10 ring atoms. Unless otherwise specified, the heterocyclic ring may be carbon or nitrogen linked.

25 Examples of suitable ring systems include one or more of cyclopentyl, cyclohexyl, phenyl, bicyclo[2.2.1]heptyl, cyclopentenyl, cyclohexenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, diazabicyclo[2.2.1]hept-2-yl, naphthyl, benzofuranyl, benzothienyl, benzodioxolyl, isoquinolinyl, quinolinyl, 1,2-dihydroquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydrobenzoxazinyl, quinazolinyl, 30 1,2,3,4-tetrahydroquinazolinyl, 2,3-dihydrobenzofuranyl, pyrazolyl, pyrazinyl, thiazolidinyl, indanyl, thienyl, isoxazolyl, pyridazinyl, thiadiazolyl, pyrrolyl, furanyl,

thiazolyl, indolyl, imidazolyl, pyrimidinyl, benzimidazolyl, triazolyl, tetrazolyl and pyridinyl.

Where reference is made to a saturated or unsaturated 5- to 6-membered heterocyclic ring,
5 it will be understood that this refers to alicyclic or aromatic rings containing five or six ring atoms, representative examples of which are listed above.

A '4- to 7-membered saturated heterocyclic ring' refers to a saturated monocyclic ring system having from 4 to 7 ring atoms in which one or more ring carbons is replaced by a
10 heteroatom selected from nitrogen, oxygen and sulphur. Unless otherwise specified, the heterocyclic ring may be carbon or nitrogen linked. Examples include pyrrolidinyl, piperidinyl, morpholinyl, tetrahydrofuranyl and piperazinyl.

m is suitably 2, 3 or 4 but is preferably 0 or 1.

15

R¹ may be cyano, hydroxyl, C₁-C₆, preferably C₁-C₄, alkyl (for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C₁-C₆, preferably C₁-C₄, alkoxy (for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy or n-hexoxy), C₁-C₆, preferably C₁-C₄, alkylsulphonyl
20 (for example, methylsulphonyl, ethylsulphonyl, n-propylsulphonyl, isopropylsulphonyl, n-butylsulphonyl, isobutylsulphonyl, tert-butylsulphonyl, n-pentylsulphonyl or n-hexylsulphonyl) or sulphonamido but is preferably halogen (e.g. chlorine, fluorine, bromine or iodine) or C₁-C₆, preferably C₁-C₄, haloalkyl (for example, trifluoromethyl or pentafluoroethyl).

25

In one embodiment, each R¹ independently represents halogen, especially fluorine or chlorine.

30

In another, preferred embodiment, m is 1 and R¹ represents halogen, especially fluorine or chlorine.

X may represent -CH₂- but preferably X represents a bond and Y represents -CH₂-.

Suitably each R^2 independently may represent halogen (e.g. chlorine, fluorine, bromine or iodine), C_1 - C_6 , preferably C_1 - C_4 , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) or C_1 - C_6 , preferably C_1 - C_4 , haloalkyl (e.g. 5 trifluoromethyl or pentafluoroethyl).

n may be 2 but is preferably 0 or 1, especially 0.

In another embodiment, n is 1 and R^2 represents halogen, especially fluorine;

10

q is preferably 1

In one embodiment, p is 0.

15

t is preferably 1

20

R^3 may suitably be halogen (for example, fluorine, chlorine, bromine or iodine), - NR^6R^7 , carboxyl or C_1 - C_6 , preferably C_1 - C_4 , alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by one or more (for example, one, two, three or four) substituents independently selected from halogen, amino, hydroxyl, C_1 - C_6 , preferably C_1 - C_4 , alkoxy (for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy or n-hexoxy), N -(C_1 - C_6 alkyl)amino (such as methylamino and ethylamino), N,N -di-(C_1 - C_6 alkyl)amino (such as di-N-methylamino, di-N-ethylamino and N-ethyl-N-methylamino), carboxy or carbamoyl.

25

In an embodiment, R^3 represents halogen (preferably fluorine or chlorine), - NR^6R^7 or C_1 - C_6 , preferably C_1 - C_4 , alkyl (especially methyl) optionally substituted by one or two substituents selected from halogen, amino or hydroxyl.

30

In a further embodiment, R^3 represents methyl, chlorine, - NH_2 , - $NHMe$, - NMe_2 , - $NHCOCH_3$ or - CH_2NH_2

R^4 may suitably represent halogen, or optionally substituted C_1 - C_6 alkyl but preferably R^4 represents hydrogen.

5 R^5 may be a saturated or unsaturated 5- to 10-membered ring system which ring system may comprise at least one ring heteroatom (for example, one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur and which may be optionally substituted one or more substituents (for example, one, two or three substituents) independently selected from halogen, cyano, oxo, nitro, hydroxyl, 10 carboxyl, $-C(O)H$, $-NR^8R^9$, $-C(O)NR^{10}R^{11}$, $-NHC(O)R^{12}$, $-NHSO_2R^{13}$, $-SO_2NR^{14}R^{15}$, $-NHC(O)NR^{16}R^{17}$, a group selected from C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 alkylsulphonyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylcarbonyl, phenylcarbonyl, C_3 - C_6 cycloalkyl, phenyl and a saturated or unsaturated 5- to 6-membered heterocyclic ring comprising at least one ring heteroatom 15 selected from nitrogen, oxygen and sulphur, each group being optionally substituted by one or more substituents independently selected from halogen, cyano, hydroxyl, carboxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy and C_1 - C_6 alkoxy carbonyl.

20 In one embodiment, R^5 is a mononcyclic or polycyclic (for example, bicyclic) unsaturated ring system containing from 5 to 10, preferably from 6 to 10, ring atoms which ring system may comprise one or two ring heteroatoms independently selected from nitrogen and oxygen (e.g. quinoliny, 1,2-dihydroquinoliny, 1,2,3,4-tetrahydroquinoliny, 2,3-dihydrobenzoxaziny, 1,2,3,4-tetrahydroquinazoliny, phenyl, naphthyl, pyridiny, benzofurany, pyrimidiny, isoquinoliny and quinazoliny), the ring system being 25 optionally substituted as recited above.

30 In a further embodiment, R^5 is a mononcyclic or polycyclic (for example, bicyclic) unsaturated carbocyclic ring system containing from 5 to 10, preferably from 6 to 10, ring atoms, the ring system being optionally substituted with one, two or three substituents as recited above.

In a particular embodiment, R⁵ represents phenyl optionally substituted with one or two substituents independently selected from -NHC(O)R¹², -NHC(O)NR¹⁶R¹⁷, hydroxyl or C₁-C₆ alkoxy.

5 In a further particular embodiment, R⁵ represents phenyl optionally substituted with one, two or three substituents independently selected from halogen, hydroxyl, or carboxyl.

In a further embodiment, R⁵ is a bicyclic unsaturated ring system containing 10 ring atoms, the ring system being substituted with one or two ring heteroatoms independently selected
10 from nitrogen and oxygen, the ring system being optionally substituted with oxo.

R⁶ and R⁷ each independently may represent C₁-C₆, preferably C₁-C₄, alkyl, optionally substituted by one or more substituents as recited above, or R₆ and R₇ together with the
15 nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring which may be optionally substituted with at least one substituent as recited above, but preferably R⁶ and R⁷ each independently represent hydrogen or C₁-C₆ alkylcarbonyl optionally substituted by one or two substituents as recited above.

In an embodiment of the invention R⁸ and R⁹ each independently represent hydrogen or a
20 group selected from C₁-C₆, preferably C₁-C₄, alkyl or C₃-C₆ cycloalkyl, optionally substituted by one or two substituents independently selected from halogen or C₁-C₆ alkoxy.

In another embodiment, R¹⁰ and R¹¹ each independently represent hydrogen or C₁-C₆ alkyl or C₃-C₆ cycloalkyl, optionally substituted by one or two substituents independently selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl; or R¹⁰ and R¹¹ together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring which may be optionally substituted with at least one substituent as recited above.

30

R¹² and R¹³ each independently preferably represent C₁-C₆ alkyl or C₃-C₆ cycloalkyl, optionally substituted by one or two substituents independently selected from halogen,

amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl.

R¹⁴ and R¹⁵ each independently preferably represent hydrogen or C₁-C₆ alkyl or C₃-C₆ cycloalkyl, optionally substituted by one or two substituents independently selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl; or R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring which may be optionally substituted with at least one substituent as recited above.

10

In another embodiment, R¹⁶ and R¹⁷ each independently represent hydrogen or C₁-C₆ alkyl or C₃-C₆ cycloalkyl, optionally substituted by one or two substituents independently selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl; or R¹⁶ and R¹⁷ together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring which may be optionally substituted with at least one substituent as recited above.

In one preferred group of compounds of formula (I) according to the invention,

m is 0 or 1;

20

R¹ is halogen;

X represents a bond and Y represents -CH₂-;

q is 1;

n is 0;

25

R³ is halogen, -NR⁶R⁷ or C₁-C₆ alkyl optionally substituted by one or two substituents selected from halogen, amino or hydroxyl;

R⁴ is hydrogen;

30

R⁵ is an unsaturated ring system containing from 5 to 10 ring atoms which ring system may comprise one or two ring heteroatoms independently selected from nitrogen and oxygen and which is optionally substituted by one or more substituents independently selected from halogen, cyano, oxo, nitro, hydroxyl, carboxyl, -C(O)H, -NR⁸R⁹, -C(O)NR¹⁰R¹¹, -NHC(O)R¹², -NHSO₂R¹³, -SO₂NR¹⁴R¹⁵, -NHC(O)NR¹⁶R¹⁷, a group selected from

C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkylsulphonyl, C₁-C₆ haloalkyl, C₁-C₆ alkylcarbonyl, phenylcarbonyl, C₃-C₆ cycloalkyl, phenyl and a saturated or unsaturated 5- to 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each 5 group being optionally substituted by one or more substituents independently selected from halogen, cyano, hydroxyl, carboxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy and C₁-C₆ alkoxy carbonyl.

Particularly preferred compounds within this group are those in which R⁵ represents phenyl optionally substituted with one or two substituents independently selected from 10 -NHC(O)R¹², -NHC(O)NR¹⁶R¹⁷, hydroxyl or C₁-C₆ alkoxy, or in which R⁵ represents phenyl optionally substituted with one, two or three substituents independently selected from halogen, hydroxyl, or carboxyl, or in which R⁵ is a bicyclic unsaturated ring system containing 10 ring atoms, the ring system being substituted with one or two ring 15 heteroatoms independently selected from nitrogen and oxygen, the ring system being optionally substituted with oxo.

It will be appreciated that the number and nature of substituents on rings in the compounds of the invention will be selected so as to avoid sterically undesirable combinations

20

Examples of preferred compounds of the invention include:

N-(2-{{(2S)-2-amino-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide;

N-(2-{{(2S)-2-amino-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-hydroxyphenyl)acetamide bis(trifluoroacetate) (salt);

N-(2-{{(2S)-2-amino-3-(5-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide;

N-(2-{{(2S)-2-amino-3-(5-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-hydroxyphenyl)acetamide bis(trifluoroacetate) (salt) ;

N-(2-{{(2S)-2-Amino-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide;

N-(2-{[(2*S*)-2-Amino-3-(1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-hydroxyphenyl)acetamide bis(trifluoroacetate) (salt);

N-(2-{[(2*S*)-2-(Acetylamino)-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide ;

5 *N*-{2-[3-Amino-2-(5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl} acetamide bis(trifluoroacetate);

N-{2-[3-Amino-2-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl} acetamide bis(trifluoroacetate);

10 *N*-{2-[3-Amino-2-(1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl} acetamide bis(trifluoroacetate);

N-{2-[3-Amino-2-(5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]phenyl} urea bis(trifluoroacetate);

N-{2-[3-Amino-2-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]phenyl} urea bis(trifluoroacetate);

15 *N*-{2-[2-Chloro-3-(5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-hydroxyphenyl} acetamide trifluoroacetate (salt);

N-{2-[2-(5-Chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl} acetamide trifluoroacetate;

5-{[(2*S*)-2-Amino-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-2*H*-1,4-benzoxazin-3(4*H*)-one;

20 8-{[(2*S*)-2-Amino-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy} quinolin-2(1*H*)-one;

5-Chloro-2-[2-chloro-3-(5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-hydroxybenzoic acid;

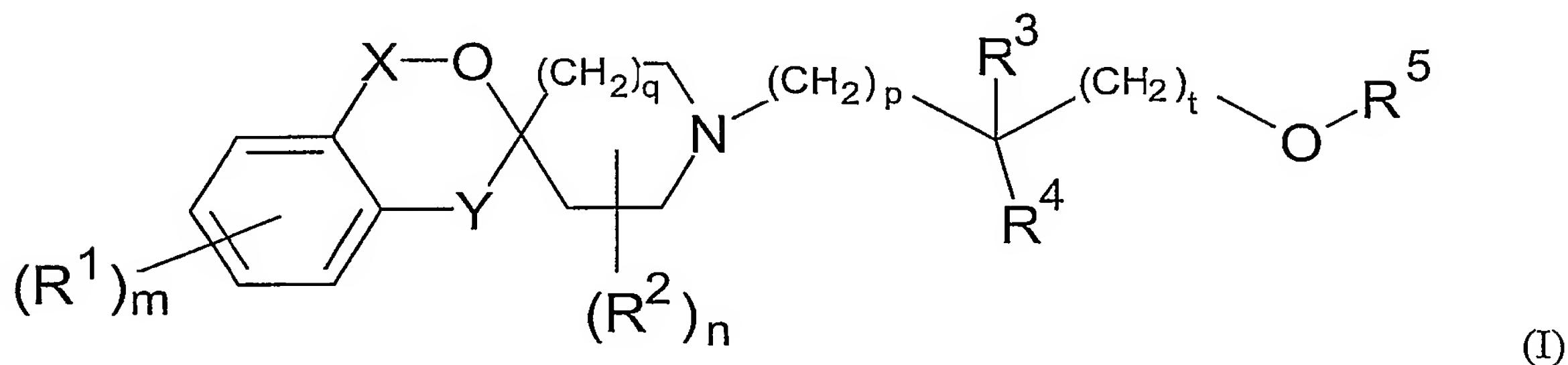
25 2-[2-Amino-3-(5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-5-chloro-4-hydroxybenzoic acid;

5-chloro-2-[3-(5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-(methylamino)propoxy]-4-hydroxybenzoic acid;

30 5-chloro-2-[3-(5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-(dimethylamino)propoxy]-4-hydroxybenzoic acid

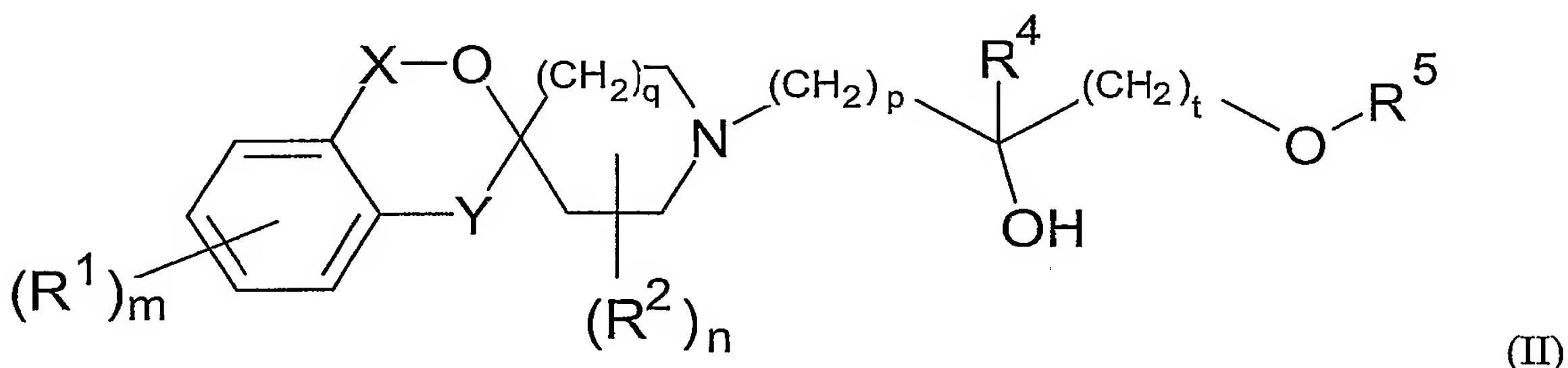
and pharmaceutically acceptable salts and solvates of any one thereof.

The present invention further provides a process for the preparation of a compound of formula (I)



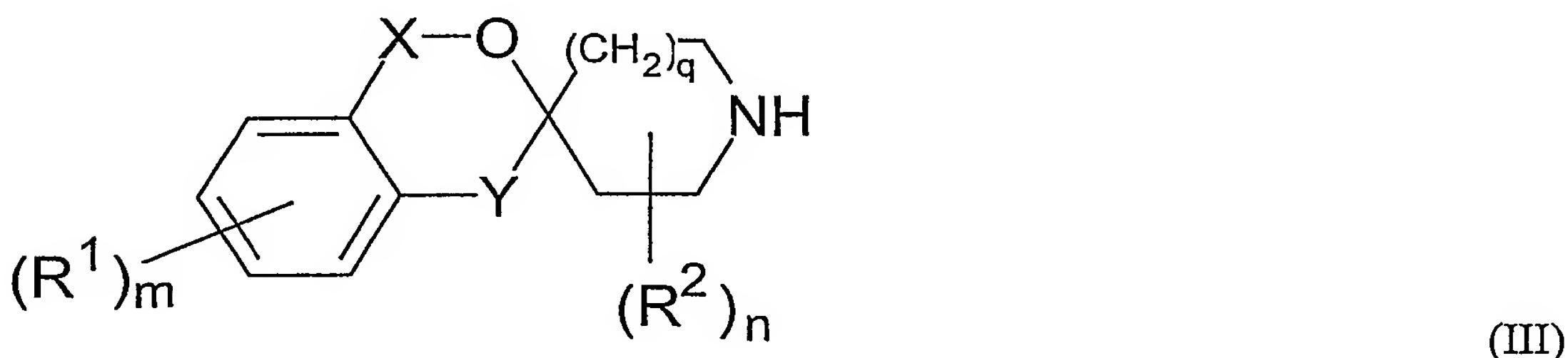
or a pharmaceutically acceptable salt or solvate thereof as defined above which comprises,

(a) converting a compound of formula (II)

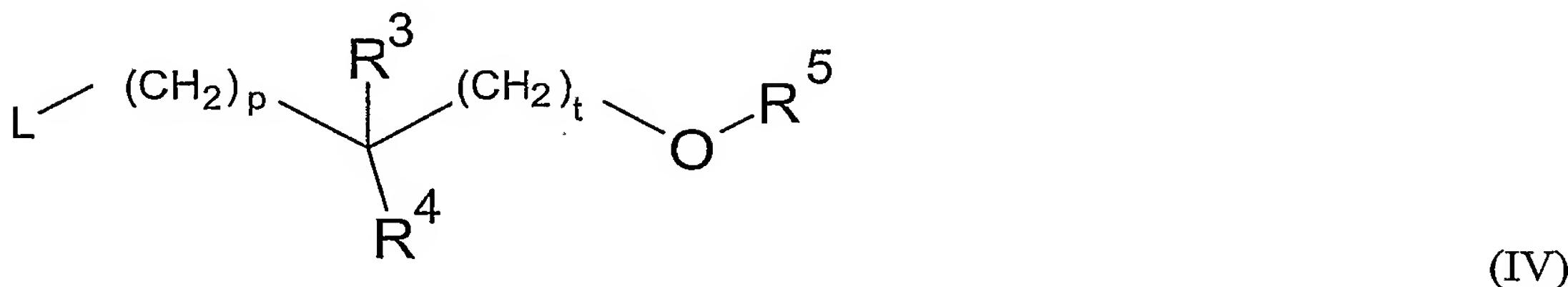


wherein R¹, m, X, Y, R², n, q, p, R⁴, t and R⁵ are as defined in formula (I), into a compound of formula (I); or

15 (b) reacting a compound of formula (III)

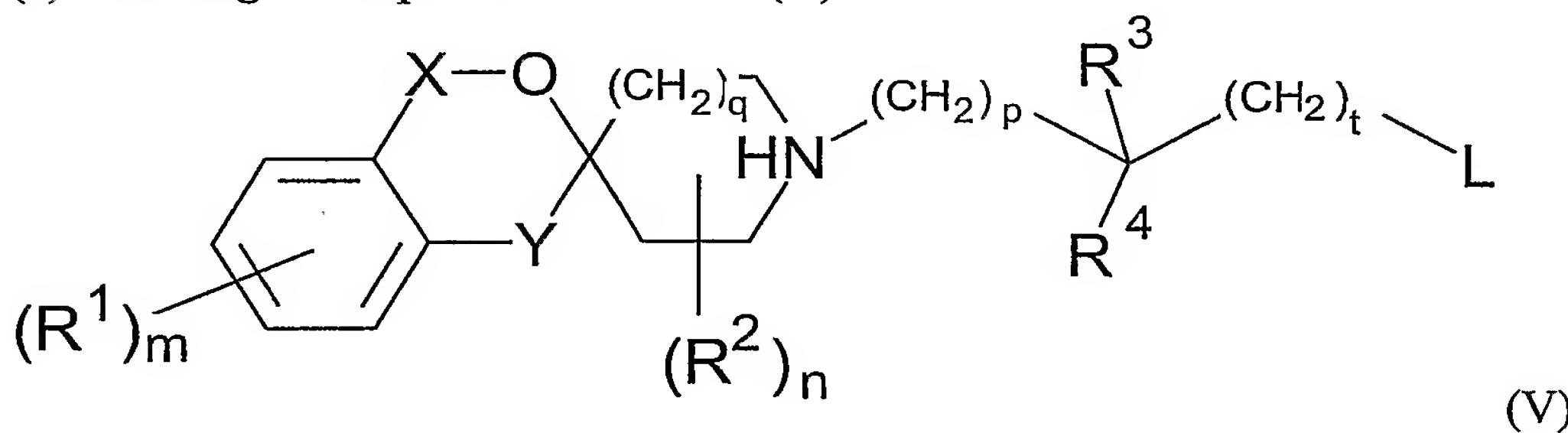


wherein R^1 , m , X , Y , R^2 , n and q are as defined for formula (I), with a compound of formula (IV)



5 wherein L is a leaving group (for example a hydroxyl group or a methylsulphonyloxy group) and p , R^3 , R^4 , t and R^5 are as defined for formula (I);

(c) reacting a compound of formula (V)



10 wherein R^1 , m , X , Y , R^2 , n , q , p , R^3 , R^4 and t are as defined for formula (I), with a compound of formula (VI)



wherein L is a leaving group (for example a methylsulphonyloxy group or nitrobenzenesulfonyloxy group) and R^5 is as defined for formula (I);

15 and optionally thereafter if necessary:

- (i) converting a compound of formula (I) into another compound of formula (I);
- (ii) removing any protecting groups; or
- (iii) forming a pharmaceutically acceptable salt or solvate.

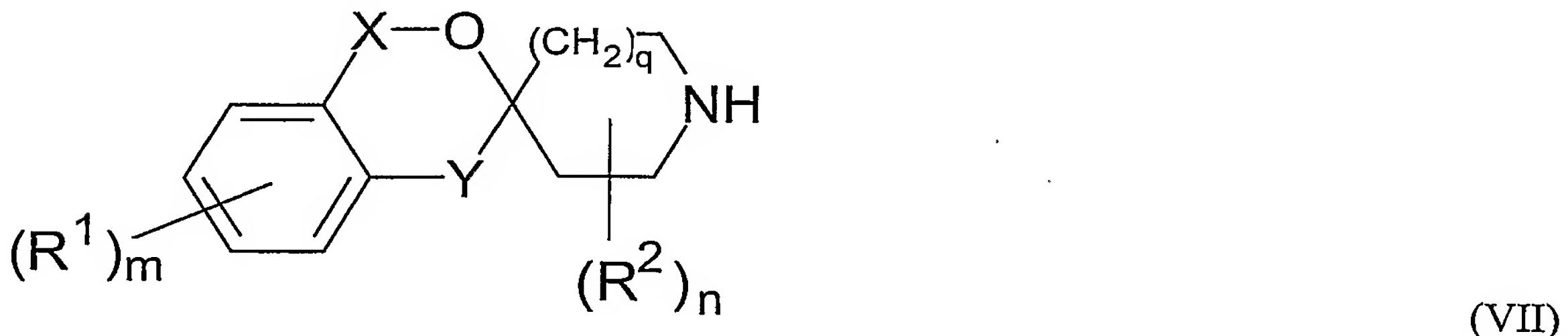
20 The processes of the invention may conveniently be carried out in a solvent, e.g. an organic solvent such as an alcohol (e.g. methanol or ethanol), a hydrocarbon (e.g. toluene) or tetrahydrofuran, dimethylformamide, N-methylpyrrolidinone, dichloromethane or

acetonitrile at a temperature of, for example, 0°C or above such as a temperature in the range from 0, 5, 10, 15 or 20°C to 100, 110 or 120°C.

Conversion of a compound of formula (II) into a compound of formula (I) according to 5 process (a) involves substituting the desired R^3 substituent for the hydroxyl group shown in the formula. This may be performed using processes known in the art such as are illustrated in the examples. An amino group, for example, may be introduced by reacting the corresponding hydroxy derivative with di-tert-butyl imidocarbonate in the presence of suitable coupling reagents such as triphenylphosphine and diethyl azodicarboxylate, and a 10 suitable solvent such as tetrahydrofuran.

Compounds of formulae (II), (III), and (IV), (V) and (VI) are either commercially available, are known in the literature or may be prepared using known techniques. Examples of preparation methods for certain of these compounds are given hereinafter in 15 the examples.

Compounds of formula (II), where p is 1, may be prepared, for example, by reacting a compound of formula (VII)



wherein R^1 , m , X , Y , R^2 , n and q are as defined in formula (I), with a compound of formula (VII)



wherein R³ and R⁵ are as defined in formula (I), and t is 1 or 2

5

Compounds of formula (VII) and (VIII) are themselves either commercially available, are known in the literature or may be prepared using known techniques.

It will be appreciated by those skilled in the art that in the processes of the present
10 invention certain functional groups such as hydroxyl or amino groups in the reagents may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups.

15 The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

20 The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

25 Compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. Enantiomerically pure forms are particularly desired.

30

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially MIP-1 α chemokine receptor) activity, and may be used

in the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS).

5 Examples of these conditions are:

(1) (the respiratory tract) airways diseases including chronic obstructive pulmonary disease (COPD) such as irreversible COPD; asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

15

(2) (bone and joints) rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

20

(3) (skin) psoriasis, atopical dermatitis, contact dermatitis and other eczematous dermatides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

25

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

30

(5) (other tissues and systemic disease) multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic

syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura;

(6) (allograft rejection) acute and chronic following, for example, transplantation of 5 kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(7) cancers, especially non-small cell lung cancer (NSCLC) and squamous sarcoma;

10 (8) diseases in which angiogenesis is associated with raised chemokine levels; and

(9) cystic fibrosis, stroke, re-perfusion injury in the heart, brain, peripheral limbs and sepsis.

15 Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

20 In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

25 The invention also provides a method of treating an inflammatory disease (e.g. rheumatoid arthritis) which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

30 The invention still further provides a method of treating an airways disease (e.g. asthma or chronic obstructive pulmonary disease) which comprises administering to a patient in need

thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary
5 with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I) may be in the range from 0.001 mg/kg to 30 mg/kg.

10 The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, 15 still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

20 The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

25 The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

30 The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

The invention will now be further illustrated by the following non-limiting examples.

¹H NMR spectra were recorded on Varian Unity Inova 400. The central solvent peak of 5 chloroform-*d* (δ_H 7.27 ppm), acetone-*d*₆ (δ_H 2.05 ppm), DMSO-*d*₆ (δ_H 2.50 ppm), or methanol-*d*₄ (δ_H 4.87 ppm) were used as internal standard.

Low resolution mass spectra and accurate mass determination were recorded on a Hewlett-Packard 1100 LC-MS system equipped with APCI /ESI ionisation chambers.

10

All solvents and commercial reagents were laboratory grade and used as received.

The nomenclature used for the compounds was generated with ACD/Name and ACD/Name Batch.

15

The abbreviations or terms used in the examples have the following meanings:

DEAD : diethyl azodicarboxylate

DMF : *N,N*-dimethylformamide

DMSO : dimethyl sulfoxide

20 THF : tetrahydrofuran

TMSCl : chlorotrimethylsilane

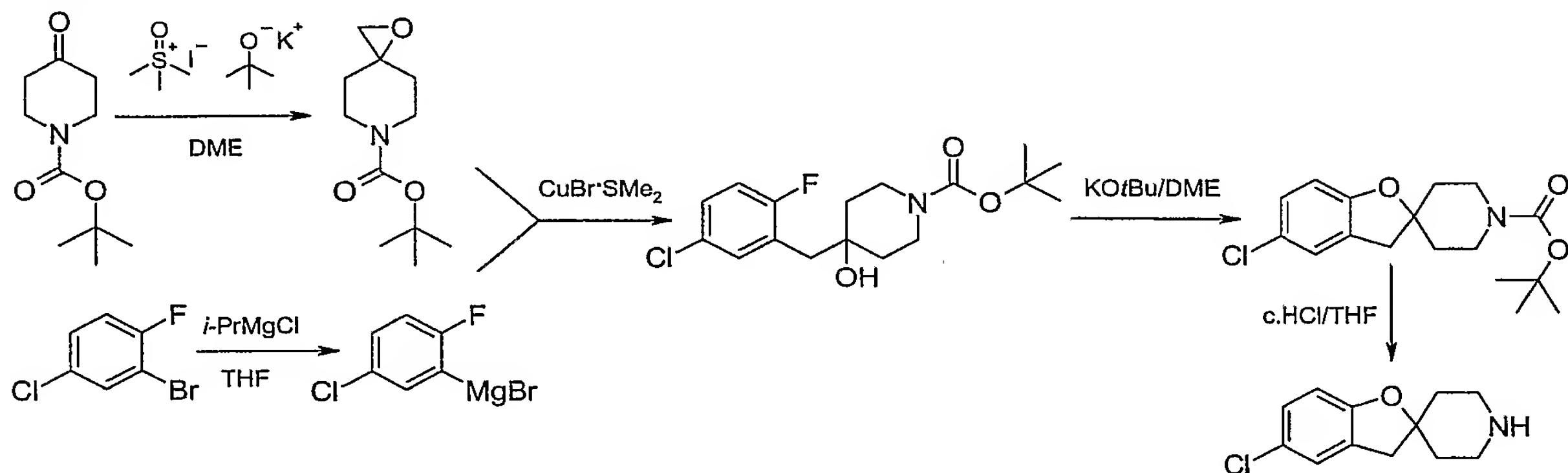
Examples

Intermediate compound: 5-Chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

Method A: This compound was prepared as described by Effland, R. R; Gardner, B. A;

5 Strupczewski, *J. J. Heterocyclic Chem.* 1981, 18, 811-814.

Method B:



Step I

10 *tert*-Butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate

Potassium *tert*-butoxide (31 g) was added to a stirred suspension of trimethylsulfoxonium iodide (60.8 g) in 1,2-dimethoxyethane (250 mL) at 20 °C. After 1 hour, the mixture was added portionwise over 30 minutes to a stirred solution of 4-oxo-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester (50 g) in 1,2-dimethoxyethane (50 mL) at 0 °C. After a further 2 hours, water (500 mL) was added and the mixture was extracted with *tert*-butyl methyl ether (2 x 500 mL). The organic extracts were washed separately with saturated sodium bicarbonate solution (250 mL). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residual oil was co-evaporated with toluene (100 mL) to give the sub-title compound (43.25g) as a solid. ¹H-NMR (CDCl₃, 400 MHz): δ 3.75-3.70 (m, 2H); 3.47-3.38 (m, 2H); 2.69 (s, 2H); 1.84-1.75 (m, 2H); 1.48-1.43 (m, 2H); 1.46 (s, 9H).

Step II

tert-Butyl 5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate

A solution of iso-propylmagnesium chloride in tetrahydrofuran (THF) (2M, 106 mL) was added dropwise over 15 minutes to a stirred solution of 2-bromo-4-chloro-1-fluorobenzene (42.5 g) in anhydrous tetrahydrofuran (250 mL) at 0 °C under nitrogen. After a further 15 minutes, a solution of *tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (43.2 g) in anhydrous tetrahydrofuran (50 mL) was added followed by copper (I) bromide dimethyl sulphide complex (0.4 g). The mixture was stirred at 40 °C for 18 hours, cooled to 20 °C, diluted with water (300 mL) and extracted with *tert*-butyl methyl ether (2 x 300 mL).
Organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residual oil was dissolved in 1,2-dimethoxypropane (200 mL).
Potassium *tert*-butoxide (22.8 g) was added and the mixture stirred at 40 °C for 16 hours then at 50 °C for 24 hours. Further potassium *tert*-butoxide (5.7 g) was added and stirring continued at 50 °C for 2 hours then at 55 °C for 4 hours. Water (500 mL) was added and the mixture extracted with *tert*-butyl methyl ether (2 x 300 mL). Organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give the sub title compound (47.45 g) as an oil. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.10 (s, 1H); 7.06 (d, 1H); 6.67 (d, 1H); 3.80-3.65 (m, 2H); 3.39 (dt, 2H); 2.94 (s, 2H); 1.93-1.85 (m, 2H); 1.67 (dt, 2H); 1.47 (s, 9H).

Step III

20 5-Chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

Concentrated hydrochloric acid (23 mL) was added to a solution of *tert*-butyl 5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidine]-1'-carboxylate (46.43 g) in tetrahydrofuran (230 mL). The mixture was stirred at 50 °C for 6 hours, cooled to 20 °C, diluted with water (230 mL) and extracted with *tert*-butyl methyl ether (2 x 230 mL). The aqueous phase was adjusted to pH >10 by addition of 50 wt.% sodium hydroxide solution and extracted with *tert*-butyl methyl ether (3 x 300 mL). Organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residual oil was dissolved in tetrahydrofuran (240 mL), concentrated hydrochloric acid (12 mL) was added and the mixture stirred at 20 °C for 16 hours. Precipitated solid was filtered and dissolved in water (100 mL). The solution was adjusted to pH >10 by addition of 50 wt.% sodium hydroxide solution and extracted with *tert*-butyl methyl ether (3 x 100 mL) to give the title

compound (13.3 g) as a solid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.13 (s, 1H); 7.04 (d, 1H); 6.65 (d, 1H); 3.03-2.98 (m, 4H); 2.84-2.78 (m, 2H); 1.87-1.83 (m, 2H); 1.76-1.69 (m, 2H). APCI-MS: m/z 224(MH^+).

5

Intermediate compound: 5-Fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

Method A:

Step I

1'-Benzyl-5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

10 To a suspension of magnesium strip (763 mg) in diethyl ether (7 mL) was added iodine (one crystal) followed by 0.4 mL of 2-(bromomethyl)-1,4-difluorobenzene under nitrogen. The reaction was initiated with a heat gun and 2-(bromomethyl)-1,4-difluorobenzene (5.0 g, 24.25 mmol) in diethyl ether (7 mL) was added slowly. After addition was completed the reaction mixture was refluxed for 100 minutes, cooled to room temperature. To this 15 reaction mixture a solution of 1-benzylpiperidin-4-one (4.57 g, 24.24 mmol) in diethyl ether (12 mL) was added dropwise with vigorous stirring. After addition was completed the mixture was left at room temperature over night. Saturated aqueous NH_4Cl solution (excess) was added and stirred at room temperature until hydrolysis was completed and the mixture was extracted with diethyl ether. The organic layer was washed with H_2O , dried 20 over Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% NH_4OH) to give intermediate 1-benzyl-4-(2,5-difluorobenzyl)piperidin-4-ol (2.74 g) containing large quantities of unknown impurities. To a suspension of NaH (55%, 1.12 g, 26.0 mmol) in toluene (10 mL) was added slowly a solution of 1-benzyl-4-(2,5-difluorobenzyl)piperidin- 25 4-ol in toluene (15 mL). After addition was completed the reaction mixture was stirred at 110 $^{\circ}\text{C}$ (in a pre heated oil bath), after 5 minutes, DMF (9 mL) was added and the mixture was refluxed for 2 hours. The reaction mixture was cooled to room temperature, water (20 mL) was added and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by silica gel flash 30 chromatography (0-1.5% methanol in dichloromethane, 0.2% NH_4OH) to give sub title compound (190 mg). $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 7.39-7.26 (m, 5H); 6.88-6.76 (m,

2H); 6.67 (dd, $J = 4.2, 8.7$ Hz, 1H); 3.59 (s, 2H); 2.99 (s, 2H); 2.68-2.47 (m, 4H); 2.03-1.94 (m, 2H); 1.86-1.76 (m, 2H).

APCI-MS: m/z 298(MH⁺).

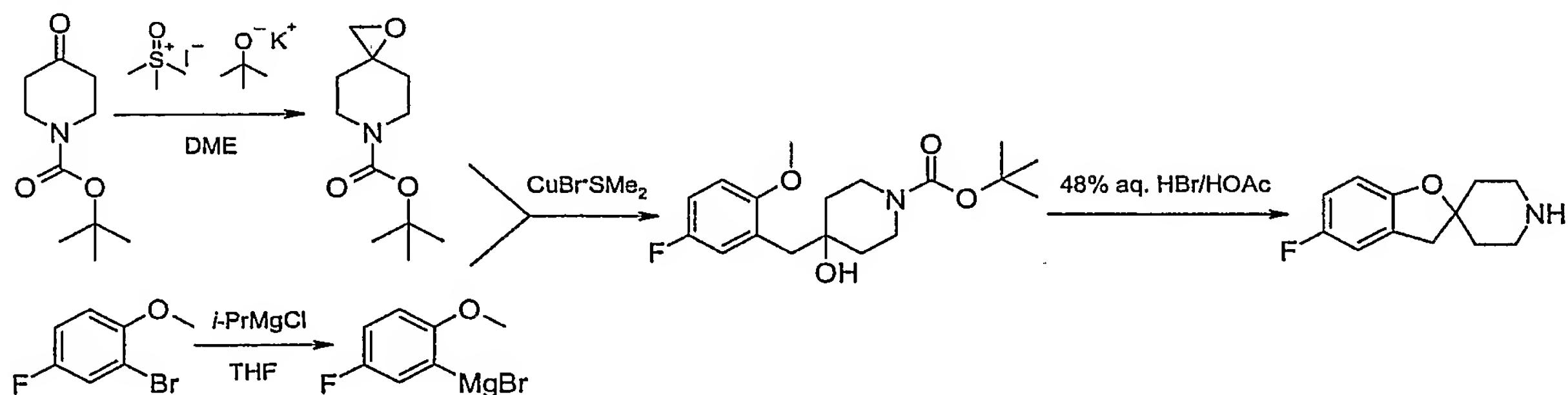
5 Step II

5-Fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

Ethyl chloroformate (65.6 mg, 0.604 mmol) was added to a solution of 1'-benzyl-5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (150 mg, 0.504 mmol) in toluene (2 mL) and the mixture was refluxed over night, cooled to room temperature, diluted by addition of toluene (10 mL), washed successively with saturated aqueous NaHCO₃ solution and water. The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was dissolved in ethanol (3.5 mL), aqueous KOH (800 mg, KOH in 0.8 mL H₂O) was added and the mixture was refluxed over night, cooled to room temperature, ethanol was removed in vacuo. Aqueous layer was extracted with diethyl ether. Combined ether layer was washed with 3N aqueous HCl. Aqueous layer was adjusted to pH 10 by addition of aqueous 3N NaOH. The basic solution was extracted with ethyl acetate. Combined organic layer was washed with water, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by HPLC (10-55% CH₃CN in H₂O, 0.1% NH₄OH) to give the title compound (49 mg). ¹H-NMR (CD₃OD, 400 MHz): δ 6.92-6.87 (m, 1H); 6.81-6.75 (m, 1H); 6.64 (dd, $J = 4.2, 8.7$ Hz, 1H); 3.08-2.98 (m, 4H); 2.89-2.81 (m, 2H); 1.91-1.83 (m, 2H); 1.78-1.69 (m, 2H).

APCI-MS: m/z 208(MH⁺).

Method B:



25 Step I

tert-Butyl4-(5-fluoro-2-methoxybenzyl)-4-hydroxypiperidine-1-carboxylate

A solution of iso-propylmagnesium chloride in tetrahydrofuran (2M, 130 mL) was added dropwise over 30 minutes to a stirred solution of 2-bromo-4-fluoroanisole (34.2 mL) in anhydrous tetrahydrofuran (400 mL) at 30 °C under nitrogen. After a further 16 hours at 30 °C, copper (I) bromide dimethyl sulphide complex (0.4 g) was added followed by solution of *tert*-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate (56.2 g) in anhydrous tetrahydrofuran (110 mL). After a further 3 hours at 30 °C, the solution was cooled to 20 °C, diluted with water (600 mL) and extracted with *tert*-butyl methyl ether (600 mL) then ethyl acetate (600 mL). Combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give crude sub-title compound (86 g) as a solid.

APCI-MS: m/z 240 [M+H-(CH₃)₂CCH₂-CO₂]⁺

Step II

5-Fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

Hydrobromic acid (48%, 60 mL) was added to a solution of the crude *tert*-butyl 4-(5-fluoro-2-methoxybenzyl)-4-hydroxypiperidine-1-carboxylate (86 g) in acetic acid (300 mL). The mixture was heated at reflux for 5 hours. Further hydrobromic acid (48%, 60 mL) was added and reflux continued for 24 hours. The mixture was cooled to room temperature, added to water (2 L) and extracted with *tert*-butyl methyl ether (2 x 500 mL). The aqueous phase was adjusted to pH >10 by addition of 50 wt.% sodium hydroxide solution and extracted with *tert*-butyl methyl ether (2L + 1L). Organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residual solid was crystallised from tetrahydrofuran / *tert*-butyl methyl ether (4:1, 500 mL) to give the title compound (20 g). ¹H-NMR (CD₃OD, 400 MHz): δ 6.92-6.87 (m, 1H); 6.81-6.75 (m, 1H); 6.64 (dd, *J* = 4.2, 8.7 Hz, 1H); 3.08-2.98 (m, 4H); 2.89-2.81 (m, 2H); 1.91-1.83 (m, 2H); 1.78-1.69 (m, 2H).

APCI-MS: m/z 208(MH⁺).

Example 1

N-(2-{{(2*S*)-2-amino-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide

Step I

(2R)-2-[(5-Methoxy-2-nitrophenoxy)methyl]oxirane

To a stirred solution of 5-methoxy-2-nitrophenol (2.11 g, 12.5 mmol) and 2(S)-oxyran-2-ylmethanol (0.926 g, 12.5 mmol) in CH_2Cl_2 (150 mL) was added polymer bound

5 triphenylphosphine (6.2 g, 18.7 mmol). The mixture was stirred at room temperature for 15 minutes, then cooled to 0 °C, DEAD (3.65 g, 18.7 mmol) was added dropwise. After addition was completed the reaction mixture was stirred at 0 °C for 2 hours. Then ice-bath was removed and the reaction mixture was stirred at room temperature over the week end. The polymer bound reagent was removed by filtration through celite. The filtrate was 10 concentrated in vacuo, *tert*-butyl methyl ether (100 mL) was added and stirred at room temperature for 30 minutes to obtain a precipitation and clear solution. The precipitate was filtered off and washed with *tert*-butyl methyl ether. The filtrate was concentrated in vacuo the residue was purified by silica gel flash chromatography (heptane/ethyl acetate) to give the sub-title compound (1.45 g).

15

¹H-NMR (CDCl_3 , 400 MHz): δ 8.00 (d, J = 9.1 Hz, 1H); 6.60 (d, J = 2.5 Hz, 1H); 6.55 (dd, J = 2.5, 9.1 Hz, 1H); 4.42 (dd, J = 2.7, 11.2 Hz, 1H); 4.13 (dd, J = 5.1, 11.2 Hz, 1H); 3.88 (s, 3H); 3.41 (m, 1H); 2.92 (m, 2H).

20 Step II

(2R)-1-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-(5-methoxy-2-nitrophenoxy)propan-2-ol

A mixture of 5-chloro-3H-spiro[1-benzofuran-2,4'-piperidine] (396 mg, 1.77 mmol) and

25 (2R)-2-[(5-methoxy-2-nitrophenoxy)methyl]oxirane (400 mg, 1.77 mmol) in ethanol (5 mL) was stirred at 88 °C for 4 hours. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH_4OH) to give the sub-title compound (700 mg).

30 ¹H-NMR (CDCl_3 , 400 MHz): δ 8.02 (d, J = 9.1 Hz, 1H); 7.12 (s, 1H); 7.07 (dd, J = 2.2, 8.5 Hz, 1H); 6.68 (d, J = 8.5 Hz, 1H); 6.58 (d, J = 2.5 Hz, 1H); 6.55 (dd, J = 2.5, 9.1 Hz, 1H); 4.26-4.12 (m, 3H); 3.90 (s, 3H); 3.00 (s, 2H); 2.98-2.65 (m, 6H); 2.06-1.82 (m, 4H).

APCI-MS: m/z 449(MH⁺).

Step III

N-(2-{{(2*R*)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide

(2*R*)-1-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-(5-methoxy-2-nitrophenoxy)propan-2-ol (700 mg, 1.56 mmol) was dissolved in ethyl acetate (35 mL), Pt/C (5%, 121 mg) was added and hydrogenated at room temperature at atmospheric pressure for 3 hours. After hydrogenation was completed, acetic anhydride (0.22 mL, 2.34 mmol) was added and the reaction mixture was stirred at room temperature for 1 hour. The catalyst was filtered off, the filtrate was concentrated in vacuo and the residue was dissolved in methanol (10 mL), 2 drops of concentrated aqueous NaOH was added and the mixture was refluxed for 3 hours, cooled to room temperature. The pH of the reaction mixture was adjusted to 2 by addition of aqueous hydrochloric acid, concentrated and the residue was purified by silica gel flash chromatography (0-4% methanol in dichloromethane, 0.2% NH₄OH) to give the sub-title compound (620 mg).

¹H-NMR (CDCl₃, 400 MHz): δ 8.18 (d, *J* = 8.8 Hz, 1H); 8.10 (br.s, 1H); 7.12 (s, 1H); 7.08 (dd, *J* = 2.2, 8.4 Hz, 1H); 6.68 (d, *J* = 8.4 Hz, 1H); 6.57-6.50 (m, 2H); 4.18 (m, 1H); 4.06 (dd, *J* = 3.3, 10.2 Hz, 1H); 3.96 (dd, *J* = 5.5, 10.2 Hz, 1H); 3.79 (s, 3H); 3.02 (s, 2H); 2.96 (m, 2H); 2.82-2.58 (m, 4H); 2.22 (s, 3H); 2.00 (m, 4H).

APCI-MS: m/z 461(MH⁺).

Step IV

N-(2-{{(2*S*)-2-amino-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide

To a mixture of *N*-(2-{{(2*R*)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide (610 mg, 1.32 mmol), triphenylphosphine (692 mg, 2.64 mmol) and di-*tert*-butyl imidodicarbonate (574 mg, 2.64 mmol) in THF (6 mL) was added DEAD (460 mg, 2.64 mmol) in THF (4 mL) dropwise at 0 °C. After addition was completed, the reaction mixture was stirred at room temperature over night. The volatiles were removed in vacuo and the residue was treated with aqueous

trifluoroacetic acid (0.4 mL of H₂O in 7.6 mL of CF₃CO₂H) at room temperature for 15 minutes. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% NH₄OH) to give the title compound (81 mg).

5

¹H-NMR (CD₃OD, 400 MHz): δ 7.66 (d, *J* = 8.8 Hz, 1H); 7.13 (m, 1H); 7.04 (dd, *J* = 2.2, 8.5 Hz, 1H); 6.65 (d, *J* = 8.5 Hz, 1H); 6.59 (d, *J* = 2.6 Hz, 1H); 6.49 (dd, *J* = 2.6, 8.8 Hz, 1H); 4.10 (dd, *J* = 3.3, 9.6 Hz, 1H); 3.90 (dd, *J* = 6.5, 9.6 Hz, 1H); 3.78 (s, 3H); 3.38 (m, 1H); 3.02 (s, 2H); 2.75-2.46 8m, 6H); 2.16 (s, 3H); 1.98-1.77 (m, 4H).

10 APCI-MS: m/z 460(MH⁺).

It also yielded *N*-(2-[3-Amino-2-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl)acetamide (84 mg) as a byproduct, see Example 8.

15 Example 2

N-(2-{[(2*S*)-2-amino-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide

To a cold (ice-water) solution of *N*-(2-{[(2*S*)-2-amino-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide (65 mg, 0.141 mmol) in CH₂Cl₂ (3 mL) was added slowly a solution of BBr₃ in CH₂Cl₂ (1 M, 0.42 mL, 0.42 mmol) under nitrogen atmosphere. After the addition was completed, the reaction mixture was stirred at 0 °C for 3.5 hours, additional 1(M) solution of BBr₃ in CH₂Cl₂ (0.2 mL) was added and the mixture was stirred at the same temperature for an additional hour, 25 methanol (2 mL) was added slowly and stirring was continued at 0 °C for 20 minutes. The volatiles were removed in vacuo and the residue was dissolved in methanol (5 mL), concentrated aqueous NH₄OH (1 mL) was added and after 5 minutes the volatiles were removed in vacuo and the residue was purified by HPLC (10-65% acetonitrile in water, 0.1% CF₃CO₂H) to give the title compound (31 mg).

30

¹H-NMR (CD₃OD, 400 MHz): δ 7.27 (d, *J* = 8.6 Hz, 1H); 7.18 (m, 1H); 7.08 (dd, *J* = 2.2, 8.6 Hz, 1H); 6.70 (d, *J* = 8.6 Hz, 1H); 6.54 (d, *J* = 2.4 Hz, 1H); 6.45 (dd, *J* = 2.4, 8.6 Hz,

1H); 4.35 (dd, $J = 3.3, 10.9$ Hz, 1H); 4.19 (dd, $J = 5.9, 10.9$ Hz, 1H); 4.04 (br.s, 1H); 3.28-2.98 (m, 8H); 2.15 (s, 3H); 2.16-2.01 (m, 4H).

APCI-MS: m/z 446(MH⁺).

5 Example 3

N-(2-{{[(2*S*)-2-amino-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl]propyl}oxy}-4-methoxyphenyl)acetamide

Step I

10 (2*R*)-2-[(5-Methoxy-2-nitrophenoxy)methyl]oxirane

To a mixture of (2*S*)-oxiran-2-ylmethanol (445 mg, 6.0 mmol), 5-methoxy-2-nitrophenol (1.02 g, 6.0 mmol) and triphenylphosphine (1.57 g, 6.0 mmol) in THF (10 mL) was added DEAD (0.95 mL, 6.0 mmol) in THF (5 mL) dropwise at 0 °C. After addition was completed the ice bath was removed and the mixture was stirred at room temperature over night. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-40% ethyl acetate in petroleum spirit) to give the sub-title compound (820 mg).

15 ¹H-NMR (CDCl₃, 400 MHz): δ 8.00 (d, $J = 9.1$ Hz, 1H); 6.60 (d, $J = 2.5$ Hz, 1H); 6.54 (dd, $J = 2.5, 9.1$ Hz, 1H); 4.41 (dd, $J = 2.7, 11.3$ Hz, 1H); 4.12 (dd, $J = 5.0, 11.3$ Hz, 1H); 3.88 (s, 3H); 3.41 (m, 1H); 2.92 (m, 2H).

20 APCI-MS: m/z 226(MH⁺).

Step II

N-{4-methoxy-2-[(2*R*)-oxiran-2-ylmethoxy]phenyl}acetamide

25 A mixture of (2*R*)-2-[(5-methoxy-2-nitrophenoxy)methyl]oxirane (620 mg, 2.75 mmol), Pd/C (10%, 250 mg), *N*-ethyl-*N*-isopropylpropan-2-amine (0.94 mL, 5.5 mmol) and acetic anhydride (0.52 mL, 5.5 mmol) in ethyl acetate (25 mL) was hydrogenated at atmospheric pressure at room temperature for 40 minutes. The catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-60% ethyl acetate in petroleum spirit) to give sub-title compound (155 mg) and 204 mg of *N*-[2-(2-hydroxypropoxy)-4-methoxyphenyl]acetamide (see example 14).

¹H-NMR (CDCl₃, 400 MHz): δ 8.22 (d, *J* = 8.8 Hz, 1H); 7.64 (br.s, 1H); 6.55-6.49 (m, 2H); 4.34 (dd, *J* = 2.5, 11.3 Hz, 1H); 3.94 (dd, *J* = 6.1, 11.3 Hz, 1H); 3.78 (s, 3H); 3.39 (m, 1H); 2.96 (t, *J* = 4.5 Hz, 1H); 2.78 (dd; *J* = 2.6, 4.8 Hz, 1H); 2.20 (s, 3H).
APCI-MS: m/z 238(MH⁺).

5

Step III

N-(2-{{[(2*R*)-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide

10 A mixture of 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (250 mg, 1.02 mmol) and *N*-(4-methoxy-2-[(2*R*)-oxiran-2-ylmethoxy]phenyl)acetamide (150 mg, 0.632 mmol) in ethanol (3 mL) was stirred at 80 °C over night. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH₄OH) to give the sub-title compound (266 mg).

15

¹H-NMR (CD₃OD, 400 MHz): δ 7.74 (d, *J* = 8.8 Hz, 1H); 6.90 (dd, *J* = 2.6, 8.2 Hz, 1H); 6.77 (m, 1H); 6.65-6.60 (m, 2H); 6.51 (dd, *J* = 2.6, 8.8 Hz, 1H); 4.17 (m, 1H); 4.09 (dd, *J* = 3.4, 9.9 Hz, 1H); 3.96 (dd, *J* = 6.2, 9.9 Hz, 1H); 3.78 (s, 3H); 3.01 (s, 2H); 2.70 (br.s, 4H); 2.61 (m, 2H); 2.15 (s, 3H); 1.97-1.81 (m, 4H).

20

APCI-MS: m/z 445(MH⁺).

Step IV

N-(2-{{[(2*S*)-2-amino-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide

25 To a mixture of *N*-(2-{{[(2*R*)-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide (260 mg, 0.58 mmol), triphenylphosphine (228 mg, 0.87 mmol) and di-*tert*-butyl imidodicarbonate (189 mg, 0.87 mmol) in THF (3 mL) was added DEAD (0.137 mL, 0.87 mmol) in THF (1.5 mL) dropwise at 0 °C. After addition was completed, the reaction mixture was stirred at room 30 temperature over night. The volatiles were removed in vacuo and the residue was treated with aqueous trifluoroacetic acid (0.2 mL of H₂O in 3.8 mL of CF₃CO₂H) at room temperature for 30 minutes. The volatiles were removed in vacuo and the residue was

purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the title compound (45 mg).).

¹H-NMR (CD₃OD, 400 MHz): δ 7.65 (d, *J* = 8.8 Hz, 1H); 6.89 (dd, *J* = 2.7, 8.1 Hz, 1H); 6.77 (m, 1H); 6.62 (dd, *J* = 4.2, 8.7 Hz, 1H); 6.60 (d, *J* = 2.6 Hz, 1H); 6.50 (dd, *J* = 2.6, 8.8 Hz, 1H); 4.10 (dd, *J* = 3.3, 9.7 Hz, 1H); 3.90 (dd, *J* = 6.6, 9.7 Hz, 1H); 3.79 (s, 3H); 3.38 (m, 1H); 3.01 (s, 2H); 2.76-2.46 (m, 6H); 2.15 (s, 3H); 1.94 (m, 2H); 1.82 (m, 2H). APCI-MS: m/z 444(MH⁺).

From this reaction mixture, *N*-{2-[3-amino-2-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl}acetamide (22 mg) was obtained as byproduct, (see example 9)

Example 4

N-(2-{{[(2*S*)-2-amino-3-(5-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-hydroxyphenyl)acetamide bis(trifluoroacetate) (salt)

To a cold (ice-water) solution of *N*-(2-{{[(2*S*)-2-amino-3-(5-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide (43 mg, 0.097 mmol) in CH₂Cl₂ (2 mL) was added a solution of BBr₃ in CH₂Cl₂ (1 M, 0.29 mL, 0.29 mmol) slowly under nitrogen atmosphere. After the addition was completed, the reaction mixture was stirred at 0 °C for 3 hours, methanol (1 mL) was added slowly and stirring was continued at 0 °C for 30 minutes. The volatiles were removed in vacuo and the residue was dissolved in methanol (5 mL), concentrated aqueous NH₄OH (1 mL) was added and after 5 minutes the volatiles were removed in vacuo and the residue was purified by HPLC (10-70% acetonitrile in water, 0.1% CF₃CO₂H) to give the title compound (25 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.26 (d, *J* = 8.6 Hz, 1H); 6.94 (dd, *J* = 2.6, 8.1 Hz, 1H); 6.81 (m, 1H); 6.67 (dd, *J* = 4.1, 8.7 Hz, 1H); 6.54 (d, *J* = 2.5 Hz, 1H); 6.45 (dd, *J* = 2.5, 8.6 Hz, 1H); 4.35 (dd, *J* = 3.4, 10.9 Hz, 1H); 4.20 (dd, *J* = 5.9, 10.9 Hz, 1H); 4.05 (m, 1H); 3.30-3.00 (m, 8H); 2.15 (s, 3H); 2.12-2.01 (m, 4H). APCI-MS: m/z 430(MH⁺).

Example 5

N-(2-{{(2S)-2-Amino-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-4-methoxyphenyl)acetamide

5

Step I

(2R)-1-(5-Methoxy-2-nitrophenoxy)-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propan-2-ol

A mixture of 3H-spiro[1-benzofuran-2,4'-piperidine]¹ (335 mg, 1.77 mmol) and (2R)-2-[(5-methoxy-2-nitrophenoxy)methyl]oxirane (400 mg, 1.77 mmol) in ethanol (5 mL) was stirred at 88 °C for 5 hours. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the sub-title compound (533 mg).

15 ¹H-NMR (CDCl₃, 400 MHz): δ 8.02 (d, *J* = 9.1 Hz, 1H); 7.16 (d, *J* = 7.7 Hz, 1H); 7.12 (d, *J* = 7.5 Hz, 1H); 6.84 (m, 1H); 6.77 (d, *J* = 8.0 Hz, 1H); 6.57 (d, *J* = 2.5 Hz, 1H); 6.54 (dd, *J* = 2.5, 9.1 Hz, 1H); 4.28-4.12 (m, 3H); 3.89 (s, 3H); 3.02 (s, 2H); 2.96 (m, 1H); 2.90-2.64 (m, 5H); 2.04 (m, 2H); 1.89 (m, 2H).

APCI-MS: m/z 415(MH⁺).

20

1: Reference; Effland, R. R.; Gardner, B. A.; Strupczewski, J. *J. Heterocyclic Chem.* 1981, 18, 811-814.

Step II

25 N-(2-{{(2R)-2-hydroxy-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-4-methoxyphenyl)acetamide

(2R)-1-(5-methoxy-2-nitrophenoxy)-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propan-2-ol (530 mg, 1.28 mmol) was hydrogenated at atmospheric pressure and room temperature in the presence of Pt/C (5%, 100 mg) in ethyl acetate (30 mL) for 4 hours.

30 Acetic anhydride (0.182 mL, 1.92 mmol) was added and the mixture was stirred at room temperature for 2 hours. The catalyst was filtered off and the filtrate was concentrated. The residue was dissolved in methanol (10 mL), conc. aqueous NaOH (4 drops) was added and

the mixture was stirred at room temperature for 20 hours. The pH of the mixture was adjusted to 2 by addition of aqueous HCl. The volalites were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% NH₄OH) to give sub-title compound (466 mg).

5

¹H-NMR (CD₃OD, 400 MHz): δ 7.74 (d, J = 8.8 Hz, 1H); 7.12 (d, J = 7.3 Hz, 1H); 7.06 (t, J = 7.9 Hz, 1H); 6.78 (t, J = 7.3 Hz, 1H); 6.68 (d, J = 7.9 Hz, 1H); 6.61 (d, J = 2.8 Hz, 1H); 6.51 (dd, J = 2.6, 8.8 Hz, 1H); 4.18 (m, 1H); 4.10 (dd, J = 3.4, 10.0 Hz, 1H); 3.97 (dd, J = 6.3, 10.0 Hz, 1H); 3.78 (s, 3H); 3.01 (s, 2H); 2.72 (br.s, 4H); 2.62 (m, 2H); 2.15 (s, 3H); 10 1.94 (m, 2H); 1.84 (m, 2H).

APCI-MS: m/z 427(MH⁺).

Step III

N-(2-{{(2*S*)-2-Amino-3-(1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-4-methoxyphenyl)acetamide

To a mixture of *N*-(2-{{(2*R*)-2-hydroxy-3-(1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-4-methoxyphenyl)acetamide (460 mg, 1.08 mmol), triphenylphosphine (566 mg, 2.16 mmol) and di-*tert*-butyl imidodicarbonate (469 mg, 2.16 mmol) in THF (5 mL) was added DEAD (376 mg, 2.16 mmol) in THF (3 mL) dropwise at 0 °C. After 20 addition was completed, the reaction mixture was stirred at room temperature over night. The volatiles were removed in vacuo and the residue was treated with aqueous trifluoroacetic acid (0.4 mL of H₂O in 7.6 mL of CF₃CO₂H) at room temperature for 15 minutes. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% NH₄OH) to give the title 25 compound (85 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.65 (d, J = 8.8 Hz, 1H); 7.13 (d, J = 7.3 Hz, 1H); 7.05 (t, J = 7.9 Hz, 1H); 6.78 (t, J = 7.3 Hz, 1H); 6.67 (d, J = 7.9 Hz, 1H); 6.60 (d, J = 2.6 Hz, 1H); 6.50 (dd, J = 2.6, 8.8 Hz, 1H); 4.11 (dd, J = 3.4, 9.7 Hz, 1H); 3.91 (dd, J = 6.5, 9.7 Hz, 30 1H); 3.78 (s, 3H); 3.40 (m, 1H); 3.01 (s, 2H); 2.78-2.48 (m, 6H); 2.15 (s, 3H); 1.94 (m, 2H); 1.84 (m, 2H).

APCI-MS: m/z 426(MH⁺).

From this reaction mixture, *N*-{2-[3-Amino-2-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl}acetamide (55 mg) was also obtained as byproduct, see example 10.

5

Example 6

N-(2-{{[(2*S*)-2-Amino-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-hydroxyphenyl)acetamide bis(trifluoroacetate) (salt)

10 To a cold (ice-water) solution of *N*-(2-{{[(2*S*)-2-amino-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide (75 mg, 0.176 mmol) in CH₂Cl₂ (3 mL) was added a solution of BBr₃ in CH₂Cl₂ (1 M, 1.0 mL, 1.0 mmol) slowly under nitrogen atmosphere. After the addition was completed, the reaction mixture was stirred at 0 °C for 3.5 hours, methanol (2 mL) was added slowly and 15 stirring was continued at 0 °C for 20 minutes. The volatiles were removed in vacuo and the residue was dissolved in methanol (5 mL), concentrated aqueous NH₄OH (1 mL) was added and after 5 minutes the volatiles were removed in vacuo and the residue was purified by HPLC (10-55% acetonitrile in water, 0.1% CF₃CO₂H) to give the title compound (45 mg).

20

¹H-NMR (CD₃OD, 400 MHz): δ 7.27 (d, *J* = 8.6 Hz, 1H); 7.17 (d, *J* = 7.3 Hz, 1H); 7.08 (t, *J* = 7.6 Hz, 1H); 6.84 (t, *J* = 7.3 Hz, 1H); 6.72 (d, *J* = 8.0 Hz, 1H); 6.53 (d, *J* = 2.4 Hz, 1H); 6.44 (dd, *J* = 2.5, 8.6 Hz, 1H); 4.35 (dd, *J* = 3.5, 10.9 Hz, 1H); 4.19 (dd, *J* = 5.8, 10.9 Hz, 1H); 4.05 (m, 1H); 3.30-3.00 (m, 8H); 2.16 (s, 3H); 2.08 (m, 4H).

25

APCI-MS: m/z 412(MH⁺).

Example 7

N-(2-{{[(2*S*)-2-(Acetylamino)-3-(5-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide

30

To a solution of *N*-(2-{{[(2*S*)-2-amino-3-(5-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide (13 mg, 0.029 mmol) in THF

(1.5 mL) was added pyridine (0.3 mL) followed by acetic anhydride (0.15 mL) and the mixture was stirred at room temperature for 2 hours. Then 0.5 mL H₂O was added and the mixture was stirred at room temperature for 30 minutes. The volatiles were removed in vacuo and co-evaporated with toluene. The residue was dissolved in methanol (3 mL) and pH was adjusted to 14 by addition of aqueous 3M NaOH. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH₄OH) to give the title compound (9 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.63 (d, *J* = 8.8 Hz, 1H); 6.89 (dd, *J* = 2.6, 8.3 Hz, 1H); 6.77 (m, 1H); 6.64-6.59 (m, 2H); 6.50 (dd, *J* = 2.6, 8.8 Hz, 1H); 4.47 (m, 1H); 4.10 (dd, *J* = 4.3, 9.6 Hz, 1H); 4.05 (dd, *J* = 5.7, 9.6 Hz, 1H); 3.78 (s, 3H); 3.00 (s, 2H); 2.74-2.52 (m, 6H); 2.16 (s, 3H); 2.02 (s, 3H); 1.93 (m, 2H); 1.81 (m, 2H).
APCI-MS: m/z 486(MH⁺).

Example 8

N-{2-[3-Amino-2-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl}acetamide bis(trifluoroacetate)

After flash chromatography on silica gel (from Example 1, step IV) this compound was purified by HPLC (10-65% CH₃CN in H₂O, 0.1% CF₃CO₂H) to give the title compound (95 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.28 (d, *J* = 8.7 Hz, 1H); 7.14 (m, 1H); 7.04 (dd, *J* = 2.2, 8.5 Hz, 1H); 6.71-6.66 (m, 2H); 6.57 (dd, *J* = 2.5, 8.7 Hz, 1H); 4.34 (d, *J* = 5.0 Hz, 2H); 3.79 (s, 3H); 3.54 (m, 1H); 3.42-3.24 (m, 2H); 3.18-2.95 (m, 6H); 2.13 (s, 3H); 2.02 (m, 4H).

APCI-MS: m/z 460(MH⁺).

Example 9

N-{2-[3-Amino-2-(5-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl}acetamide bis(trifluoroacetate)

After flash chromatography on silica gel this compound, (from Example 3, step IV) was purified by HPLC (10-70% CH₃CN in H₂O, 0.1% CF₃CO₂H) to give the title compound (16 mg).

5 ¹H-NMR (CD₃OD, 400 MHz): δ 7.30 (d, J = 8.6 Hz, 1H); 6.92 (dd, J = 2.7, 8.2 Hz, 1H); 6.82-6.75 (m, 1H); 6.69-6.64 (m, 2H); 6.57 (dd, J = 2.6, 8.7 Hz, 1H); 4.34-4.23 (m, 2H); 3.82 (s, 3H); 3.42 (m, 1H); 3.22 (m, 2H); 3.08-2.79 (m, 6H); 2.13 (s, 3H); 2.07-2.84 (m, 4H).
APCI-MS: m/z 444(MH⁺).

10

Example 10

N-{2-[3-Amino-2-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl}acetamide bis(trifluoroacetate)

15 After flash chromatography on silica gel this compound, (from Example 5, step III), was purified by HPLC (10-65% CH₃CN in H₂O, 0.1% CF₃CO₂H) to give the title compound (55 mg).

20 ¹H-NMR (CD₃OD, 400 MHz): δ 7.30 (d, J = 8.7 Hz, 1H); 7.15 (d, J = 7.2 Hz, 1H); 7.07 (t, J = 7.4 Hz, 1H); 6.81 (t, J = 7.3 Hz, 1H); 6.71 (d, J = 7.9 Hz, 1H); 6.68 (d, J = 2.6 Hz, 1H); 6.58 (dd, J = 2.6, 8.7 Hz, 1H); 4.32 (m, 2H); 3.81 (s, 3H); 3.48 (m, 1H); 3.40-3.22 (m, 2H); 3.14-2.88 (m, 6H); 2.13 (s, 3H); 2.00 (m, 4H).
APCI-MS: m/z 426(MH⁺).

25

Example 11

N-{2-[3-Amino-2-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]phenyl}urea bis(trifluoroacetate)

Step I

30 *N*-(2-Hydroxyphenyl)urea

2-Aminophenol (1.09 g, 10.0 mmol) was dissolved in aqueous HCl (1 M, 10 mL), then ammonium acetate was added until pH became 5, potassium isocyanate (892 mg, 11.0

mmol) in H₂O (3 mL) was added with vigorous stirring at room temperature. After addition was completed the reaction mixture was stirred at room temperature over night. The precipitate was filtered off, washed with water and the precipitate was collected to give the sub-title compound (1.3 g).

5

¹H-NMR (DMSO-d₆, 400 MHz): δ 10.00 (br.s, 1H); 8.00 (br.s, 1H); 7.80 (d, J = 8.0 Hz, 1H); 6.80-6.65 (m, 3H); 6.22 (br.s, 2H).

APCI-MS: m/z 153(MH⁺).

10 Step II

N-{2-[(2*R*)-Oxiran-2-ylmethoxy]phenyl}urea

To a mixture of (2*S*)-oxiran-2-ylmethanol (296 mg, 4.0 mmol), *N*-(2-hydroxyphenyl)urea (609 mg, 4.0 mmol) and triphenylphosphine (1.05 g, 4.0 mmol) in THF (10 mL) was dropwise added DEAD (697 mg, 4.0 mmol) in THF (3 mL) at room temperature. After addition was completed the reaction mixture was stirred at room temperature over night.

The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-80% ethyl acetate in petroleum spirit) to give sub-title compound (336 mg).

20 ¹H-NMR (DMSO-d₆, 400 MHz): δ 8.08 (m, 1H); 7.82 (s, 1H); 6.98 (m, 1H); 6.85 (m, 2H); 6.24 (br.s, 2H); 4.37 (dd, J = 2.5, 11.7 Hz, 1H); 3.89 (dd, J = 6.6, 11.7 Hz, 1H); 3.38 (m, 1H); 2.87 (t, J = 4.7 Hz, 1H); 2.75 (dd, J = 2.7, 5.0 Hz, 1H).

Step III

25 *N*-(2-{[(2*R*)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)urea

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (161 mg, 0.72 mmol) and *N*-{2-[(2*R*)-oxiran-2-ylmethoxy]phenyl}urea (150 mg, 0.72 mmol) in ethanol (2 mL) was stirred at 88 °C for 5 hours. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the sub-title compound (220 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.95 (m, 1H); 7.14 (m, 1H); 7.04 (dd, J = 2.2, 8.4 Hz, 1H); 7.00-6.86 (m, 3H); 6.66 (d, J = 8.5 Hz, 1H); 4.23-4.16 (m, 1H); 4.09 (dd, J = 3.8, 9.9 Hz, 1H); 4.00 (dd, J = 6.1, 9.9 Hz, 1H); 3.02 (s, 2H); 2.78-2.55 (m, 6H); 1.94 (m, 2H); 1.84 (m, 2H).

5 APCI-MS: m/z 432(MH⁺).

Step IV

N-{2-[3-Amino-2-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]phenyl}urea bis(trifluoroacetate)

10 To a mixture of *N*-(2-{(2*R*)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy)phenyl)urea (190 mg, 0.439 mmol), triphenylphosphine (173 mg, 0.658 mmol) and di-*tert*-butyl imidodicarbonate (143 mg, 0.658 mmol) in THF (3 mL) was added DEAD (115 mg, 0.658 mmol) in THF (2 mL) dropwise at 0 °C. After addition was completed, the reaction mixture was stirred at room temperature over night. The volatiles 15 were removed in vacuo and the residue was treated with aqueous trifluoroacetic acid (0.2 mL of H₂O in 3.8 mL of CF₃CO₂H) at room temperature for 20 minutes. The volatiles were removed in vacuo and the residue was purified by HPLC (10-70% CH₃CN in H₂O, 0.1% CF₃CO₂H) to give the title compound (10 mg).

20 ¹H-NMR (CD₃OD, 400 MHz): δ 7.63 (m, 1H); 7.17-6.95 (m, 5H); 6.68 (d, J = 8.4 Hz, 1H); 4.44-4.28 (m, 2H); 3.50 (m, 1H); 3.31 (m, 3H); 3.18-2.87 (m, 5H); 2.02 (m, 4H). APCI-MS: m/z 431(MH⁺).

Example 12

25 *N*-{2-[3-Amino-2-(5-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]phenyl}urea bis(trifluoroacetate)

Step I

26 *N*-(2-{(2*R*)-3-(5-Fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy)phenyl)urea

5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (182 mg, 0.88 mmol) and *N*-{2-[(2*R*)-oxiran-2-ylmethoxy]phenyl}urea (183 mg, 0.88 mmol) in ethanol (2 mL) was stirred at 88 °C over night. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH₄OH) to give the 5 sub-title compound (250 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.94 (m, 1H); 7.00-6.87 (m, 4H); 6.78 (m, 1H); 6.63 (dd, *J* = 4.2, 8.8 Hz, 1H); 4.23-4.16 (m, 1H); 4.10 (dd, *J* = 3.8, 9.9 Hz, 1H); 4.00 (dd, *J* = 6.1, 9.9 Hz, 1H); 3.02 (s, 2H); 2.78-2.55 (m, 6H); 1.93 (m, 2H); 1.83 (m, 2H).
10 APCI-MS: m/z 416(MH⁺).

Step II

N-{2-[3-Amino-2-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]phenyl}urea bis(trifluoroacetate)
15 To a mixture of *N*-(2-[(2*R*)-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)phenylurea (200 mg, 0.48 mmol), triphenylphosphine (189 mg, 0.72 mmol) and di-*tert*-butyl imidodicarbonate (156 mg, 0.72 mmol) in THF (3 mL) was added DEAD (125 mg, 0.72 mmol) in THF (2 mL) dropwise at 0 °C. After addition was completed, the reaction mixture was stirred at room temperature over night. The volatiles 20 were removed in vacuo and the residue was treated with aqueous trifluoroacetic acid (0.2 mL of H₂O in 3.8 mL of CF₃CO₂H) at room temperature for 20 minutes. The volatiles were removed in vacuo and the residue was purified by HPLC (10-70% CH₃CN in H₂O, 0.1% CF₃CO₂H) to give the title compound (15 mg).

25 ¹H-NMR (CD₃OD, 400 MHz): δ 7.63 (dd, *J* = 1.2, 8.0 Hz, 1H); 7.15-7.05 (m, 2H); 6.97 (m, 1H); 6.91 (dd, *J* = 2.6, 8.2 Hz, 1H); 6.78 (m, 1H); 6.65 (dd, *J* = 4.2, 8.8 Hz, 1H); 4.37 (dd, *J* = 5.5, 10.7 Hz, 1H); 4.28 (m, 1H); 3.43 (m, 1H); 3.30 (m, 3H); 3.17-2.78 (m, 5H); 2.07-1.88 (m, 4H).
30 APCI-MS: m/z 415(MH⁺).

Example 13

N-{2-[2-Chloro-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-hydroxyphenyl}acetamide trifluoroacetate (salt)

Step I

5 (1*Z*)-1-(2,4-Dihydroxyphenyl)ethanone oxime

1-(2,4-Dihydroxyphenyl)ethanone (4.5 g, 29.6 mmol) was dissolved in pyridine (17 mL). Hydroxylamine hydrochloride (2.1 g, 29.6 mmol) was added in small portions over 10 minutes. The reaction mixture was stirred at room temperature over night, partitioned between ethyl acetate and H₂O. The organic layer was washed with H₂O and 0.2 M aqueous HCl respectively. The oily residue was treated with H₂O, evaporated in vacuo to yield a white semi-solid residue which was treated with toluene and then evaporated in vacuo to give the sub-title compound (4.8 g) as a white solid.

10 APCI-MS: m/z 168(MH⁺).

15 Step II

2-Methyl-1,3-benzoxazol-6-ol

To a cooled (ice-water) solution of (1*Z*)-1-(2,4-dihydroxyphenyl)ethanone oxime (9.7 g, 57.7 mmol) and dimethylacetamide (11 mL) in acetonitrile (65 mL) was added phosphorous oxychloride (5.6 mL, 60.3 mmol) dropwise. The temperature was not allowed 20 to exceed 10 °C during the reaction. After 1 hour stirring at room temperature the yellow slurry was poured into a mixture of aqueous NaHCO₃ and ice. The resulting precipitate was filtered off and dried to give the sub-title compound (6.3 g).

25 ¹H-NMR (DMSO-d₆, 400 MHz): δ 9.68 (br.s, 1H); 7.38 (d, *J* = 8.5 Hz, 1H); 6.94 (d, *J* = 2.2 Hz, 1H); 6.74 (dd, *J* = 8.5, 2.2 Hz, 1H); 2.50 (s, 3H).

APCI-MS: m/z 150(MH⁺).

Step III

2-Methyl-1,3-benzoxazol-6-yl acetate

30 A slurry of 2-methyl-1,3-benzoxazol-6-ol (7.1 g, 48.7 mmol) in THF (150 mL) was cooled to 10 °C and triethylamine (11.3 mL, 81.3 mmol) was added in one portion, followed by the addition of acetyl chloride (5.8 mL, 81.3 mmol) in small portions. After addition was

completed the reaction mixture was stirred at room temperature over night, partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4 , filtered and concentrated in vacuo to give sub-title compound (8.2 g).

5 $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ 7.65 (d, 1H); 7.47 (s, 1H); 7.15 (d, 1H); 2.60 (s, 3H); 2.24 (s, 3H).

Step IV

4-(Acetylamino)-3-hydroxyphenyl acetate

10 To a solution of 2-methyl-1,3-benzoxazol-6-yl acetate (5.05 g, 28.8 mmol) in THF (100 mL) a mixture of trifluoroacetic acid/water (4 mL/10 mL) was added. The reaction mixture was stirred at room temperature for 16 hours, saturated aqueous NaHCO_3 (150 mL) was added. The mixture was extracted with ethyl acetate, dried over Na_2SO_4 , filtered and concentrated in vacuo to give sub-title compound (4.0 g) as a crude product.

15

Step V

4-(acetylamino)-3-[(2S)-oxiran-2-ylmethoxy]phenyl acetate

20 A mixture of 4-(acetylamino)-3-hydroxyphenyl acetate (669 mg, 3.2 mmol), (2S)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (748 mg, 2.9 mmol) and Cs_2CO_3 ((1.05 g, 3.2 mmol) in 1-methyl-pyrrolidinone (10 mL) was stirred at room temperature over night. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4 , filtered and concentrated in vacuo to give a yellow oil which was suspended in methanol/diethyl ether. The precipitate was filtered off and dried to give the sub-title compound (296 mg).

25

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 8.40 (d, 1H); 7.80 (s, 1H); 6.78 (m, 2H); 4.39 (m, 1H); 3.92 (m, 1H); 3.40 (m, 1H); 2.98 (t, 1H); 2.80 (m, 1H); 2.25 (s, 3H); 2.20 (s, 3H).

Step VI

30 *N*-(2-{{(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl}oxy}-4-hydroxyphenyl)acetamide

5-Chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (335.5 mg, 1.5 mmol) and 4-(acetylamino)-3-[(2*S*)-oxiran-2-ylmethoxy]phenyl acetate (398 mg, 1.5 mmol) in ethanol (3 mL) was stirred at 80 °C for 24 hours. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% NH₄OH) to give the sub-title compound (302 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.57 (d, *J* = 8.7 Hz, 1H); 7.14 (s, 1H); 7.04 (dd, *J* = 2.3, 8.5 Hz, 1H); 6.65 (d, *J* = 8.5 Hz, 1H); 6.48 (d, *J* = 2.5 Hz, 1H); 6.36 (dd, *J* = 2.6, 8.7 Hz, 1H); 4.20-4.13 (m, 1H); 4.05 (dd, *J* = 3.4, 9.8 Hz, 1H); 3.93 (dd, *J* = 6.2, 9.8 Hz, 1H); 3.02 (s, 2H); 2.77-2.55 (m, 6H); 2.14 (s, 3H); 1.93 (m, 2H); 1.84 (m, 2H).
APCI-MS: m/z 447(MH⁺).

Step VII

N-(2-[2-Chloro-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-hydroxyphenyl)acetamide trifluoroacetate (salt)

To a solution of oxalyl chloride (22 mg, 0.173 mmol) in dichloromethane (1 mL) was added a solution of DMSO (26 mg, 0.332 mmol) in dichloromethane (0.5 mL) slowly at -78 °C. After 10 minutes a solution of *N*-(2-[(2*S*)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy)-4-hydroxyphenyl)acetamide (25 mg, 0.056 mmol) in dichloromethane (0.5 mL) was added slowly. After 25 minutes a solution of diethylaminosulfur trifluoride (DAST) (0.1 mL) in dichloromethane (0.5 mL) was added slowly and the reaction mixture was stirred at -78 °C for 4 hours, Et₃N (0.2 mL) was added and after 5 minutes cooling bath was removed and the reaction mixture was diluted by addition of dichloromethane (5 mL), washed with water. The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by HPLC (10-70% CH₃CN in H₂O, 0.1% CF₃CO₂H) to give the title compound as a byproduct (2 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 7.32 (d, *J* = 8.7 Hz, 1H); 7.15 (s, 1H); 7.06 (dd, *J* = 2.2, 8.5 Hz, 1H); 6.68 (d, *J* = 8.5 Hz, 1H); 6.51 (d, *J* = 2.5 Hz, 1H); 6.41 (dd, *J* = 2.5, 8.6 Hz, 1H); 4.54 (br.s, 1H); 4.28 (d, *J* = 5 Hz, 2H); 3.24-2.83 (m, 8H); 2.13 (s, 3H); 1.98 (m, 4H).
APCI-MS: m/z 465(MH⁺).

Example 14

N-{2-[2-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl}acetamide trifluoroacetate

5

Step I

N-[2-(2-Hydroxypropoxy)-4-methoxyphenyl]acetamide

This was obtained during reaction in Example 3, Step II, as a byproduct (204 mg).

10 $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 8.02 (d, J = 8.6 Hz, 1H); 7.85 (br.s, 1H); 6.48 (m, 2H); 4.22 (m, 1H); 3.98 (dd, J = 2.9, 9.9 Hz, 1H); 3.84 (m, 1H); 3.78 (s, 3H); 2.15 (s, 3H); 1.29 (d, J = 6.5 Hz, 3H).
APCI-MS: m/z 240(MH^+).

15

Step II

N-{2-[2-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl}acetamide

16 *N*-[2-(2-Hydroxypropoxy)-4-methoxyphenyl]acetamide (92 mg, 0.38 mmol) was dissolved in dichloromethane (3 mL), cooled to 0 °C and Et_3N (0.076 mL, 0.547 mmol) was added followed by methanesulfonyl chloride (52 mg, 0.456 mmol). The reaction mixture was stirred at 0 °C for 2 hours, diluted by addition of dichloromethane (20 mL), washed successively with saturated aqueous NaHCO_3 and H_2O . The organic layer was dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was taken in ethanol (3 mL), 5-chloro-3H-spiro[1-benzofuran-2,4'-piperidine] (85 mg, 0.38 mmol) was added and the mixture was refluxed for 40 h. The reaction mixture was cooled to room temperature and the volatiles were removed in vacuo. The residue was dissolved in ethyl acetate (30 mL), washed successively with saturated aqueous NaHCO_3 and water, dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by HPLC (10-70% CH_3CN in H_2O , 0.1% $\text{CF}_3\text{CO}_2\text{H}$) to give the title compound (35 mg).

30

$^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.20 (m, 1H); 7.18 (d, J = 8.6 Hz, 1H); 7.11 (dd, J = 2.1, 8.5 Hz, 1H); 6.77 (d, J = 8.5 Hz, 1H); 6.71 (d, J = 2.6 Hz, 1H); 6.61 (dd, J = 2.6, 8.7 Hz,

1H); 4.46 (dd, J = 3.4, 12.2 Hz, 1H); 4.36 (dd, J = 8.6, 12.2 Hz, 1H); 3.96 (m, 1H); 3.81 (s, 3H); 3.69-3.40 (m, 4H); 3.12 (s, 2H); 2.45-2.17 (m, 4H); 1.50 (d, J = 7.0 Hz, 3H). APCI-MS: m/z 445(MH⁺).

5 Example 15

5-{[(2*S*)-2-Amino-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-2*H*-1,4-benzoxazin-3(4*H*)-one

Step I:

10 2-Aminobenzene-1,3-diol

A mixture of 2-nitrobenzene-1,3-diol (5 g, 32.2 mmol) and 10% Pd on charcoal (230 mg) in ethanol (100 ml) were hydrogenated with H₂ at atmospheric pressure overnight. The reaction mixture was filtered through celite. Ethanol was removed by evaporation to yield the subtitled compound (4 g, 99%).

15

¹H-NMR (400 MHz, DMSO-*d*₆): δ 8.81 (br.s, 2H), 6.24 (m, 3H), 3.81 (br.s, 2H).

APCI-MS: m/z 126.0 (MH⁺).

Step II:

20 2-Chloro-*N*-(2,6-dihydroxyphenyl)acetamide

KH₂PO₄ (17.2 g, 126.3 mmol) and K₂HPO₄ (8.2 g, 35.7 mmol) in 188 ml of distilled water were deoxygenated by passing argon through the mixture for 0.5 hour. 2-Aminobenzene-1,3-diol (1 g, 8.0 mmol) was added to the buffer solution and chloroacetyl chloride (0.64 ml, 8.0 mmol) was added slowly to the reaction mixture. After addition was completed, the reaction mixture was stirred at room temperature for 1.5 hours. Water was removed by freeze-drying and the residue was dissolved in 20% MeOH in DCM. The insoluble salt was removed by filtration, the solvent was evaporated to give the subtitled compound which was used without purification in the next step.

30 APCI-MS: m/z 202.0 (MH⁺).

Step III:

5-Hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one

2-Chloro-*N*-(2,6-dihydroxyphenyl)acetamide (1.99 g, 9.88 mmol) was dissolved in 150 ml of 10% aqueous K_2CO_3 and the solution was heated to 40°C for 45 minutes. After cooling and neutralization with 2M HCl the reaction mixture was extracted with ethyl acetate.

Drying with $MgSO_4$ and evaporation of solvent afforded crude material (0.54 g, overall yield from Steps II and III 41 %).

10 APCI-MS: m/z 166.0 (MH^+).

Step IV

Methyl *N*-(*tert*-butoxycarbonyl)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-L-alanine

15 To a cold (ice-water bath) suspension of 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (1.03 g, 5 mmol) and methyl *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanate (1.64 g, 5 mmol) in dichloromethane (20 mL) was added triethyl amine (0.697 mL, 5 mmol). After a clear solution was obtained, the reaction mixture was kept at 5 °C for 48 h. Then it was diluted by addition of dichloromethane (50 mL), washed with water (10 mL), dried over Na_2SO_4 , 20 filtered and concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-1.5 % methanol in dichloromethane containing 0.2% ammonia) to give the subtitle compound (1.2 g).

25 1H -NMR ($CDCl_3$, 400 MHz): δ 6.85 (m, 1H); 6.78 (m, 1H); 6.64 (dd, J = 4.2, 8.7 Hz, 1H); 5.40 (br.s, 1H); 4.35 (br.s, 1H); 3.76 (s, 3H); 2.99 (s, 2H); 2.80-2.43 (m, 6H); 1.93 (m, 2H); 1.77 (m, 2H); 1.48 (s, 9H).

APCI-MS: m/z 409 (MH^+).

Step V

tert-Butyl [(1*S*)-2-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-1-(hydroxymethyl)ethyl]carbamate

To a suspension of LiBH₄ (77 mg, 3.51 mmol) in THF (10 mL) was added a solution of methyl *N*-(*tert*-butoxycarbonyl)-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-L-alanine (1.2 g, 2.93 mmol) in THF (15 mL) at 0 °C. After the addition was completed, stirring was continued at 0 °C for 4 h, then at room temperature over night. The reaction mixture was cooled again to 0 °C, and a saturated aqueous NH₄Cl solution (15 mL) was added slowly. After 1 h, the reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with water (10 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane containing 0.2% ammonia) to give title compound (376 mg).

¹H-NMR (CD₃OD, 400 MHz): δ 6.90 (m, 1H); 6.77 (m, 1H); 6.62 (dd, *J* = 4.2, 8.7 Hz, 1H); 3.78 (m, 1H); 3.56 (m, 2H); 3.00 (s, 2H); 2.68 (br.s, 4H); 2.50 (m, 2H); 1.94 (m, 2H); 1.82 (m, 2H); 1.48 (s, 9H).

APCI-MS: m/z 381 (MH⁺).

Step VI

(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl 3-nitrobenzenesulfonate

To a stirred solution of *tert*-butyl [(1*S*)-2-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-1-(hydroxymethyl)ethyl]carbamate (300 mg, 0.79 mmol) in DCM (20 ml) was added triethylamine (120 mg, 1.18 mmol). The mixture was cooled to 0 °C, and a solution of 3-nitrobenzenesulfonyl chloride (250 mg, 1.18 mmol) in DCM (5 ml) was added. The mixture was stirred at 0 °C for 4 h, then allowed to warm to room temperature and stirred overnight. Then the reaction mixture was washed with water (30 ml) and aq. NaHCO₃ (1 M, 30 ml), and dried over Na₂SO₄. The solvent was removed i.vac. to afford a colourless oil (155 mg, 35 %), which was used in the next step without purification.

¹H-NMR (400 MHz, CDCl₃): δ 8.73 (m, 1H), 8.30 - 8.21 (m, 2H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.06 (br. d, *J* = 5.8 Hz, 1H), 6.91 - 6.78 (m, 2H), 6.64 (dd, *J* = 8.7, 4.1 Hz, 1H), 5.00 (m, 2H), 4.87 (m, 1H), 4.71 (m, 1H), 4.40 (m, 2H), 3.96 (d, *J* = 12.0 Hz, 1H), 3.64 (m, 3H), 3.07 (s, 2H), 2.16 (s, 4H), 1.41 (s, 9H)

5

Step VII

5-{[(2*S*)-2-Amino-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-2*H*-1,4-benzoxazin-3(4*H*)-one

A mixture of (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl 3-nitrobenzenesulfonate (77 mg, 0.14 mmol), 5-Hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one (23 mg, 0.14 mmol) and Cs₂CO₃ (68 mg, 0.21 mmol) in dry DMF (2 ml) was stirred at room temperature for 36 h. Then the mixture was partitionned between DCM (50 ml) and water (50 ml), and the layers were separated. The organic layer was washed with water, and the solvent was removed i.vac. The residue was dissolved in TFA (95 % in water, 2 ml), and the solution was stirred at room temperature for 1 h. Then the reaction mixture was diluted with ethyl acetate (30 ml), and washed with aq. NaHCO₃ (1 M, 30 ml). The solvent was removed i.vac., the residue purified by HPLC (10-40% CH₃CN in H₂O, 0.6 % NH₃) to give the title compound (12 mg, 21 %).

¹H-NMR (CD₃OD, 400 MHz): δ 6.91 (m, 2H), 6.78 (td, *J* = 8.9, 2.7 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 2H), 6.62 (m, 2H), 4.54 (s, 2H), 4.14 (dd, *J* = 9.6, 3.3 Hz, 1H), 3.94 (dd, *J* = 9.5, 6.4 Hz, 1H), 3.43 (m, 1H), 3.02 (s, 2H), 2.77 - 2.55 (m, 4H), 2.52 (d, *J* = 7.0 Hz, 2H), 1.95 (m, 2H), 1.85 (m, 2H).

APCI-MS: m/z 428 (MH⁺).

25

Example 16

8-{[(2*S*)-2-Amino-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}quinolin-2(1*H*)-one

30

Step I:

8-Hydroxyquinolin-2(*1H*)-one

Quinolin-8-ol 1-oxide (20 g, 124 mmol) in acetic anhydride (200 ml) was stirred at 90 °C for 5 hours. Then the reaction mixture was poured into water/ice mixture (1.5 L), and made neutral by addition of conc. aq. NH₃. The precipitate formed was collected by filtration and 5 washed with water. The crude product was purified by suspending in propan-2-ol and addition of petroleum ether to give 2-oxo-1,2-dihydroquinolin-8-yl acetate. 2-Oxo-1,2-dihydroquinolin-8-yl acetate was heated in conc. aq. HCl (200 ml) at 90 °C for 4 hours. The reaction mixture was poured into ice-cold water (400 ml), and the precipitate formed was collected by filtration and washed with water. Recrystallization from propan-2-ol / 10 petroleum ether afforded the subtitle compound (14.1 g, 70 %).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 10.46 (s, 1H), 10.21 (s, 1H), 7.84 (d, *J* = 9.5 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.7 Hz, 1H), 6.95 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.48 (d, *J* = 9.5 Hz, 1H)

15 APCI-MS: m/z 162 (MH⁺).

Step II

8-{{(2*S*)-2-Amino-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}quinolin-2(*1H*)-one

20 Prepared from 8-Hydroxyquinolin-2(*1H*)-one as described for 5-{{(2*S*)-2-Amino-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-2*H*-1,4-benzoxazin-3(4*H*)-one (Example 15, Step VII).

¹H-NMR (CD₃OD, 400 MHz): δ 7.96 (d, *J* = 9.4 Hz, 1H), 7.28 (dd, *J* = 7.0, 2.1 Hz, 1H), 7.20 (m, 2H), 6.90 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.78 (td, *J* = 8.9, 2.7 Hz, 1H), 6.65 (d, *J* = 9.4 Hz, 1H), 6.62 (m, 1H), 4.27 (dd, *J* = 9.6, 3.3 Hz, 1H), 4.08 (dd, *J* = 9.5, 6.4 Hz, 1H), 3.52 (m, 1H), 3.02 (s, 2H), 2.78 - 2.60 (m, 4H), 2.58 (d, *J* = 7.1 Hz, 2H), 1.95 (m, 2H), 1.85 (m, 2H).

APCI-MS: m/z 424 (MH⁺).

Example 17

5-Chloro-2-[2-chloro-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-hydroxybenzoic acid

5 Step I:

Methyl 5-chloro-2,4-dihydroxybenzoate

Prepared from methyl 2,4-dihydroxybenzoate using the procedure described by Anderson, W. K., et al., *J. Med. Chem.* **1996**, *39*, 46 – 55.

10 $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 10.85 (s, 1H), 7.84 (s, 1H), 6.63 (s, 1H), 5.99 (s, 1H), 3.95 (s, 3H)

Step II:

Methyl 5-chloro-2-hydroxy-4-[(4-methoxybenzyl)oxy]benzoate

15 To a solution of methyl 5-chloro-2,4-dihydroxybenzoate (0.41 g, 2 mmol) in acetone were added 1-(chloromethyl)-4-methoxybenzene (0.32 g, 2 mmol) and K_2CO_3 (0.28 g, 2 mmol). The reaction mixture was heated with reflux for 3 days, than cooled to room temperature. The inorganic material was removed by filtration. The solvent was distilled in vacuo, and the residue was recrystallized from methanol to afford white solid (0.37 g, 60 %).

20

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 10.89 (s, 1H), 7.82 (s, 1H), 7.37 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.56 (s, 1H), 5.09 (s, 2H), 3.92 (s, 3H), 3.82 (s, 3H)

Step III:

25 Methyl 5-chloro-4-[(4-methoxybenzyl)oxy]-2-[(2S)-oxiran-2-ylmethoxy]benzoate
A solution of methyl 5-chloro-2-hydroxy-4-[(4-methoxybenzyl)oxy]benzoate (0.37 g, 1.16 mmol), (2S)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (0.30 g, 1.16 mmol) and caesium carbonate (0.45 g, 1.4 mmol) in dimethylformamide (15 mL) was stirred at room temperature overnight. The mixture was partitioned between water and ethyl acetate, and the organic phase was washed twice with water and once with brine, and finally

concentrated. The crude material was purified by flash chromatography on silica gel (eluent: ethyl acetate/n-heptane), yielding the titled compound (0.33, 74%).

¹H-NMR (CDCl₃, 400 MHz): δ 7.91 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 6.92 (dd, *J* = 6.7, 2.0 Hz, 2H), 6.66 (s, 1H), 5.14 (m, 2H), 4.33 (dd, *J* = 11.4, 2.6 Hz, 1H), 3.98 (dd, *J* = 11.5, 5.1 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.36 (m, 1H), 2.93 - 2.87 (m, 2H)

APCI-MS: m/z 379 (MH⁺)

Step IV

Methyl 5-chloro-2-[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoate trifluoroacetate (salt)

A solution of 5-chloro-3H-spiro[1-benzofuran-2,4'-piperidine] (100 mg, 0.45 mmol) and methyl 5-chloro-4-[(4-methoxybenzyl)oxy]-2-[(2S)-oxiran-2-ylmethoxy]benzoate (170 mg, 0.45 mmol) in ethanol (5 mL) was refluxed for 6 h. The solvent was distilled off under reduced pressure. The residue was purified by HPLC (eluent: [acetonitrile /water + 0.1 % TFA]) to afford a colourless solid (218 mg, 67 %).

APCI-MS: m/z 602 (MH⁺)

Step V:

5-chloro-2-[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride

To a mixture of methyl 5-chloro-2-[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoate

trifluoroacetate salt (220 mg, 0.3 mmol) in ethanol (10 mL) was added a solution of potassium hydroxide (4 g) and water (4 mL). The mixture was stirred at room temperature for 3 hours, pH was adjusted to 1 with aqueous HCl (37 %), extracted with ethyl acetate, dried with sodium sulphate. Volatiles were removed in vacuo, the subtitle compound (180 mg) required no further purification.

APCI-MS: m/z 588 (MH⁺)

Step VI:

5-chloro-2-[2-chloro-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-[(4-methoxybenzyl)oxy]benzoic acid

To a stirred suspension of 5-chloro-2-[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy]-4-[(4-methoxybenzyl)oxy]benzoic acid hydrochloride (0.623 g, 1 mmol) in dry THF (50 ml) was added thionyl chloride (0.187 g, 1.5 mmol). The reaction mixture was stirred at room temperature overnight, then quenched with water (100 ml), and extracted with ethyl acetate (3 x 75 ml). The combined organic extracts were dried over Na₂SO₄, and the solvent was removed i.vac.. The residue was purified by HPLC (eluent: [acetonitrile /water + 0.1 % TFA]) to afford the subtitle compound as trifluoroacetate salt (134 mg, 19 %).

APCI-MS: m/z 608 (MH⁺)

Step VII:

5-Chloro-2-[2-chloro-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-hydroxybenzoic acid

To a solution of 5-chloro-2-[2-chloro-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-[(4-methoxybenzyl)oxy]benzoic acid trifluoroacetate salt (45 mg, 0.062 mmol) in DCM (2 ml) was added trifluoroacetic acid (95 % in water, 1 ml), and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed i.vac, the residue purified by HPLC (eluent: [acetonitrile /water + 0.1 % TFA]) to afford the title compound as trifluoroacetate salt (25 mg, 67 %).

¹H-NMR (400 MHz, acetone-*d*₆): δ 7.91 (s, 1H), 7.22 (m, 1H), 7.13 (m, 2H), 6.76 (d, *J*=8.5 Hz, 1H), 5.08 (tt, *J*=7.3, 4.8 Hz, 1H), 4.62 (dd, *J*=9.8, 4.8 Hz, 1H), 4.35 (dd, *J*=9.7, 7.3 Hz, 1H), 4.09 (dd, *J*=13.8, 7.4 Hz, 1H), 3.90 (dd, *J*=13.7, 4.6 Hz, 2H), 3.75 (m, 1H), 3.61 (m, 2H), 3.20 (s, 2H), 2.50 (m, 2H), 2.23 (m, 2H)

APCI-MS: m/z 488 (MH⁺)

Example 18

2-[2-Amino-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-5-chloro-4-hydroxybenzoic acid

5-Chloro-2-[2-chloro-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-[(4-methoxybenzyl)oxy]benzoic acid trifluoroacetate salt (see Example 17, Step VI) (35 mg, 0.048 mmol) was dissolved in a solution of NH₃ in methanol (7 M, 1 ml) and stirred at room temperature for 3 days. The volatiles were removed i.vac., the residue dissolved in DCM (1 ml), and TFA (95 % in water, 0.5 ml) was added. The solution was stirred at room temperature for 2 h, then the solvent was removed i.vac.. The residue was purified by HPLC (eluent: [acetonitrile /water + 0.1 % TFA]) to afford the title compound as bistrifluoroacetate salt (15 mg, 44 %).

¹⁵ ¹H-NMR (400 MHz, acetone-*d*₆): δ 7.90 (s, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 7.10 (s, 1H), 7.08 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 4.53 (dd, *J* = 10.7, 3.2 Hz, 1H), 4.35 (dd, *J* = 10.6, 4.6 Hz, 1H), 3.66 – 3.48 (m, 3H), 3.23 – 3.03 (m, 4H), 2.94 (m, 1H), 2.83 (m, 1H), 2.12 – 1.94 (m, 4H, partially covered with the signal of the solvent).

APCI-MS: m/z 467 (MH⁺)

Example 19

5-chloro-2-[3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-(methylamino)propoxy]-4-hydroxybenzoic acid

5-Chloro-2-[2-chloro-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-[(4-methoxybenzyl)oxy]benzoic acid trifluoroacetate salt (see Example 17, Step VI) (35 mg, 0.048 mmol) was dissolved in a solution of methylamine in ethanol (33 %wt., 1 ml) and stirred at room temperature for 3 days, then at 40 °C for 24 h. The volatiles were removed i.vac., the residue dissolved in DCM (1 ml), and TFA (95 % in water, 0.5 ml) was added. The solution was stirred at room temperature for 2 h, then the

solvent was removed i.vac.. The residue was purified by HPLC (eluent: [acetonitrile /water + 0.1 % TFA]) to afford the title compound as bistrifluoroacetate salt (24 mg, 70 %).

¹H-NMR (400 MHz, acetone-*d*₆): δ 7.92 (s, 1H), 7.29 (s, 1H), 7.17 (d, *J* = 2.0 Hz, 1H), 7.09 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 4.61 (d, *J* = 6.0 Hz, 2H), 3.98 (m, 1H), 3.83 (dd, *J* = 13.0, 4.1 Hz, 1H), 3.73 (dd, *J* = 13.1, 6.9 Hz, 1H), 3.40 – 3.22 (m, 4H), 3.11 (s, 2H), 2.93 (s, 3H), 2.13 – 2.03 (m, 4H, partially covered with the signal of solvent). APCI-MS: m/z 481 (MH⁺)

10 Example 20

5-chloro-2-[3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-(dimethylamino)propoxy]-4-hydroxybenzoic acid

5-Chloro-2-[2-chloro-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-[(4-methoxybenzyl)oxy]benzoic acid trifluoroacetate salt (see Example 17, Step VI) (35 mg, 0.048 mmol) was dissolved in a solution of dimethylamine in ethanol (33 %wt., 1 ml) and stirred at room temperature for 3 days, then at 40 °C for 36 h. The volatiles were removed i.vac., the residue dissolved in DCM (1 ml), and TFA (95 % in water, 0.5 ml) was added. The solution was stirred at room temperature for 2 h, then the solvent was removed i.vac.. The residue was purified by HPLC (eluent: [acetonitrile /water + 0.1 % TFA]) to afford the title compound as bistrifluoroacetate salt (19 mg, 54 %).

¹H-NMR (400 MHz, acetone-*d*₆): δ 7.90 (s, 1H), 7.37 (s, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 7.08 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 4.49 (dd, *J* = 9.9, 5.2 Hz, 2H), 4.43 (dd, *J* = 9.7, 7.2 Hz, 2H), 3.85 (m, 1H), 3.76 (m, 2H), 3.16 (s, 6H), 3.20 – 2.86 (m, 6H), 2.01 – 1.86 (m, 4H).

APCI-MS: m/z 495 (MH⁺)

THP-1 Chemotaxis Assay

Introduction

The assay measures the chemotactic response elicited by MIP-1 α chemokine in the human 5 monocytic cell line THP-1. Compounds are evaluated by their ability to depress the chemotactic response to a standard concentration of MIP-1 α chemokine.

Methods

Culture of THP-1 cells

10 Cells are thawed rapidly at 37°C from frozen aliquots and resuspended in a 25 cm flask containing 5 ml of RPMI-1640 medium supplemented with Glutamax and 10% heat inactivated fetal calf serum without antibiotics (RPMI+10%HIFCS). At day 3 the medium is discarded and replaced with fresh medium.

15 THP-1 cells are routinely cultured in RPMI-1640 medium supplemented with 10% heat inactivated fetal calf serum and glutamax but without antibiotics. Optimal growth of the cells requires that they are passaged every 3 days and that the minimum subculture density is 4×10^5 cells/ml.

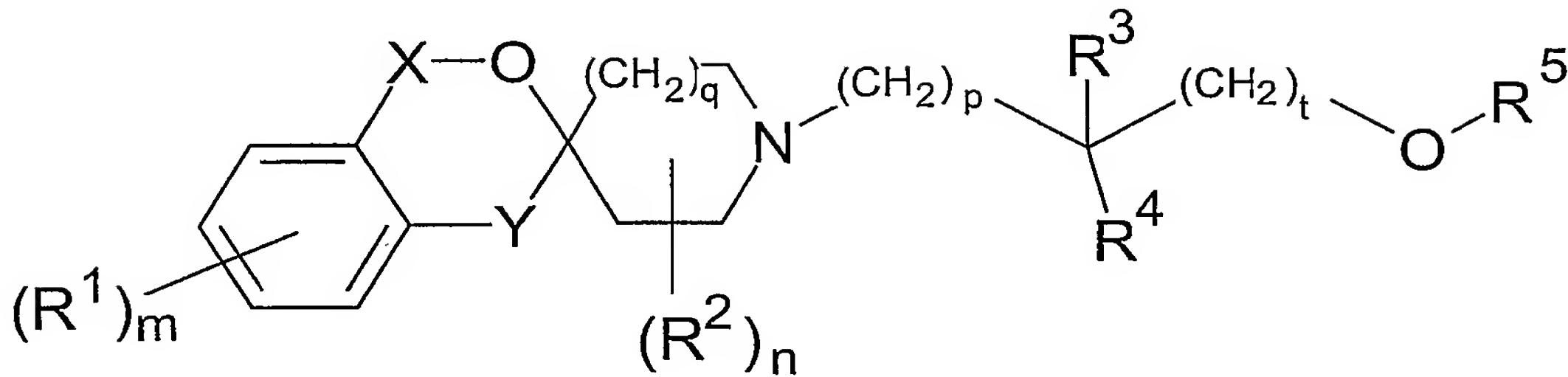
20 Chemotaxis assay

Cells are removed from the flask and washed by centrifugation in RPMI + 10%HIFCS + glutamax. The cells are then resuspended at 2×10^7 cells/ml in fresh medium (RPMI + 10%HIFCS + glutamax) to which is added calcein-AM (5 μ l of stock solution to 1 ml to give a final concentration of 5×10^{-6} M). After gentle mixing the cells are incubated at 37°C 25 in a CO₂ incubator for 30 minutes. The cells are then diluted to 50 ml with medium and washed twice by centrifugation at 400xg. Labelled cells are then resuspended at a cell concentration of 1×10^7 cells/ml and incubated with an equal volume of MIP-1 α antagonist (10^{-10} M to 10^{-6} M final concentration) for 30 minutes at 37°C in a humidified CO₂ incubator.

Chemotaxis is performed using Neuroprobe 96-well chemotaxis plates employing 8 μ m filters (cat no. 101-8). Thirty microlitres of chemoattractant supplemented with various concentrations of antagonists or vehicle are added to the lower wells of the plate in triplicate. The filter is then carefully positioned on top and then 25 μ l of cells preincubated with the corresponding concentration of antagonist or vehicle is added to the surface of the filter. The plate is then incubated for 2 hours at 37°C in a humidified CO₂ incubator. The cells remaining on the surface are then removed by adsorption and the whole plate is centrifuged at 2000 rpm for 10 minutes. The filter is then removed and the cells that have migrated to the lower wells are quantified by the fluorescence of cell associated calcein-AM. Cell migration is then expressed in fluorescence units after subtraction of the reagent blank and values are standardized to % migration by comparing the fluorescence values with that of a known number of labelled cells. The effect of antagonists is calculated as % inhibition when the number of migrated cells is compared with vehicle.

CLAIMS

1. A compound of formula



wherein

m is 0, 1, 2, 3 or 4;

10 each R¹ independently represents halogen, cyano, hydroxyl, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulphonyl or sulphonamido (-SO₂NH₂); X represents a bond or -CH₂- and Y represents a bond or -CH₂-, provided that X and Y do not both simultaneously represent a bond or -CH₂-;

n is 0, 1 or 2;

15 each R² independently represents halogen, C₁-C₆ alkyl or C₁-C₆ haloalkyl;

q is 0 or 1;

p is 0, 1 or 2;

R³ represents a group selected from halogen, NR⁶R⁷, carboxyl or C₁-C₆ alkyl wherein said C₁-C₆ alkyl group is optionally substituted by one or more halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl;

R⁴ represents hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl or halogen;

t is 0, 1 or 2, provided that p and t are not both 0;

R⁵ represents a saturated or unsaturated 5- to 10-membered ring system which ring system may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by one or more substituents independently selected from halogen, cyano, oxo, nitro, hydroxyl, carboxyl, -C(O)H, -NR⁸R⁹,

-C(O)NR¹⁰R¹¹, -NHC(O)R¹², -NHSO₂R¹³, -SO₂NR¹⁴R¹⁵, -NHC(O)NR¹⁶R¹⁷, a group selected from C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkylsulphonyl, C₁-C₆ haloalkyl, C₁-C₆ alkylcarbonyl, phenylcarbonyl, C₃-C₆ cycloalkyl, phenyl and a saturated or unsaturated 5- to 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted by one or more substituents independently selected from halogen, cyano, hydroxyl, carboxyl, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy and C₁-C₆ alkoxy carbonyl;

R⁶ and R⁷ each independently represent hydrogen or a group selected from C₁-C₆ alkyl and C₁-C₆ alkylcarbonyl, each of which may be optionally substituted by one or more substituents selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy, carbamoyl or C₁-C₆ alkoxy carbonyl, or R₆ and R₇ together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring which may be optionally substituted by one or more substituent selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy, carbamoyl or C₁-C₆ alkoxy carbonyl;

R⁸, R⁹, R¹⁰, R¹¹ each independently represent hydrogen or a group selected from C₁-C₆ alkyl or C₃-C₆ cycloalkyl, each group being optionally substituted by one or more substituents independently selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl; or R¹⁰ and R¹¹, together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring which may be optionally substituted with at least one substituent selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl;

R¹² represents hydrogen or a group selected from C₁-C₆ alkyl or C₃-C₆ cycloalkyl, each group being optionally substituted by one or more substituents independently selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl;

R¹³ represents a group selected from C₁-C₆ alkyl or C₃-C₆ cycloalkyl, each group being optionally substituted by one or more substituents independently selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl;

R¹⁴, R¹⁵, R¹⁶ and R¹⁷ each independently represent hydrogen or a group selected from C₁-C₆ alkyl or C₃-C₆ cycloalkyl, each group being optionally substituted by one or more substituents independently selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl; or R¹⁴ and R¹⁵, or R¹⁶ and R¹⁷, together with the nitrogen atom to which they are attached each independently form a 4- to 7-membered saturated heterocyclic ring which may be optionally substituted with at least one substituent selected from halogen, amino, hydroxyl, C₁-C₆ alkoxy, N-(C₁-C₆ alkyl)amino, N,N-di-(C₁-C₆ alkyl)amino, carboxy or carbamoyl;

15

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 wherein X represents a bond and Y represents -CH₂-.

20 3. A compound according to claim 1 or claim 2 wherein q is 1.

4. A compound according to any one of claims 1 to 3 wherein m is 0 or 1 and R¹ represents halogen.

5. A compound according to any one of claims 1 to 4 wherein n is 0.

25

6. A compound according to any one of claims 1 to 5 wherein R³ represents halogen, -NR⁶R⁷ or C₁-C₆ alkyl optionally substituted by one or two substituents selected from halogen, amino or hydroxyl

30 7. A compound according to any one of claims 1 to 6 wherein R⁴ represents hydrogen.

8. A compound according to any one of claims 1 to 7 wherein R⁵ represents a saturated or unsaturated 5- to 10-membered ring system which ring system may comprise one, two, three or four ring heteroatoms independently selected from nitrogen, oxygen and sulphur and which may be optionally substituted one two or three substituents independently selected from halogen, cyano, oxo, nitro, hydroxyl, carboxyl, -C(O)H, -NR⁸R⁹,

5 -C(O)NR¹⁰R¹¹, -NHC(O)R¹², -NHSO₂R¹³, -SO₂NR¹⁴R¹⁵, -NHC(O)NR¹⁶R¹⁷, a group

selected from C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio,

C₁-C₆ alkylsulphonyl, C₁-C₆ haloalkyl, C₁-C₆ alkylcarbonyl, phenylcarbonyl, C₃-C₆

cycloalkyl, phenyl and a saturated or unsaturated 5- to 6-membered heterocyclic ring

10 comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted by one or more substituents independently selected from halogen, cyano, hydroxyl, carboxyl, C₁-C₆ alkyl, C₁-C₆ cycloalkyl, C₁-C₆ alkoxy and C₁-C₆ alkoxycarbonyl.

15 9. A claim according to any one of claims 1 to 8 wherein R⁵ represents phenyl, wherein said phenyl is optionally substituted with one or two substituents independently selected

from -NHC(O)R¹², -NHC(O)NR¹⁶R¹⁷, hydroxyl or C₁-C₆ alkoxy, or wherein said phenyl is optionally substituted with one, two or three substituents independently selected from halogen, hydroxyl, or carboxyl.

20 10. A compound according to claim 1 selected from:

N-(2-{{(2S)-2-amino-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-4-methoxyphenyl)acetamide;

N-(2-{{(2S)-2-amino-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-4-hydroxyphenyl)acetamide bis(trifluoroacetate) (salt);

N-(2-{{(2S)-2-amino-3-(5-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-4-methoxyphenyl)acetamide;

N-(2-{{(2S)-2-amino-3-(5-fluoro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-4-hydroxyphenyl)acetamide bis(trifluoroacetate) (salt) ;

30 N-(2-{{(2S)-2-Amino-3-(1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl}oxy}-4-methoxyphenyl)acetamide;

N-(2-{{(2*S*)-2-Amino-3-(1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-hydroxyphenyl)acetamide bis(trifluoroacetate) (salt);

N-(2-{{(2*S*)-2-(Acetylamino)-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide ;

5 *N*-{{2-[3-Amino-2-(5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl}acetamide bis(trifluoroacetate);

N-{{2-[3-Amino-2-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl}acetamide bis(trifluoroacetate);

10 *N*-{{2-[3-Amino-2-(1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl}acetamide bis(trifluoroacetate);

N-{{2-[3-Amino-2-(5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]phenyl}urea bis(trifluoroacetate);

N-{{2-[3-Amino-2-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]phenyl}urea bis(trifluoroacetate);

15 *N*-{{2-[2-Chloro-3-(5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-hydroxyphenyl}acetamide trifluoroacetate (salt);

N-{{2-[2-(5-Chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-methoxyphenyl}acetamide trifluoroacetate;

20 5-{{(2*S*)-2-Amino-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}-2*H*-1,4-benzoxazin-3(4*H*)-one;

8-{{(2*S*)-2-Amino-3-(5-fluoro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propyl]oxy}quinolin-2(1*H*)-one;

5-Chloro-2-[2-chloro-3-(5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-4-hydroxybenzoic acid;

25 2-[2-Amino-3-(5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)propoxy]-5-chloro-4-hydroxybenzoic acid;

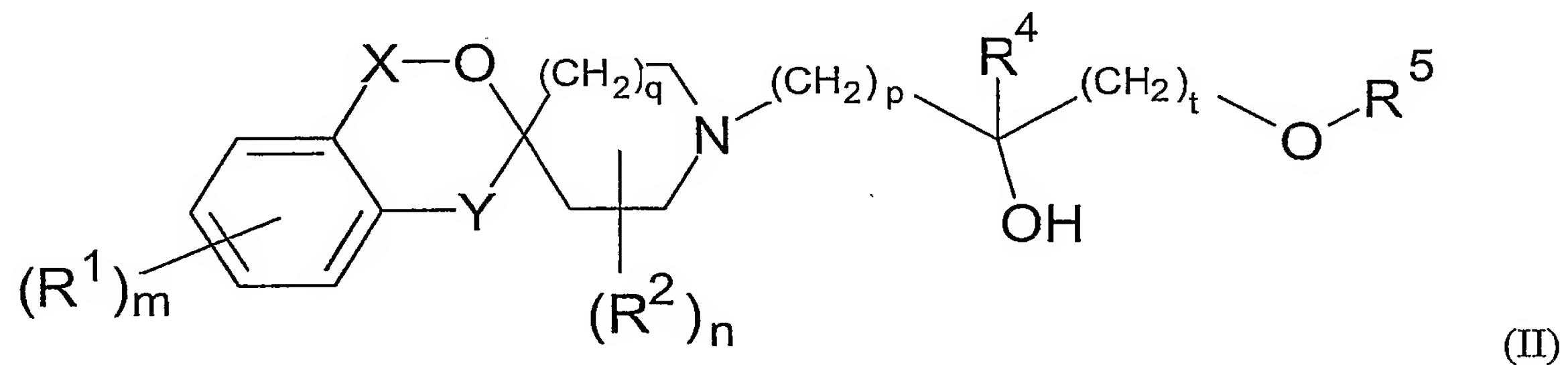
5-chloro-2-[3-(5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-(methylamino)propoxy]-4-hydroxybenzoic acid;

30 5-chloro-2-[3-(5-chloro-1*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-(dimethylamino)propoxy]-4-hydroxybenzoic acid

and pharmaceutically acceptable salts and solvates of any one thereof.

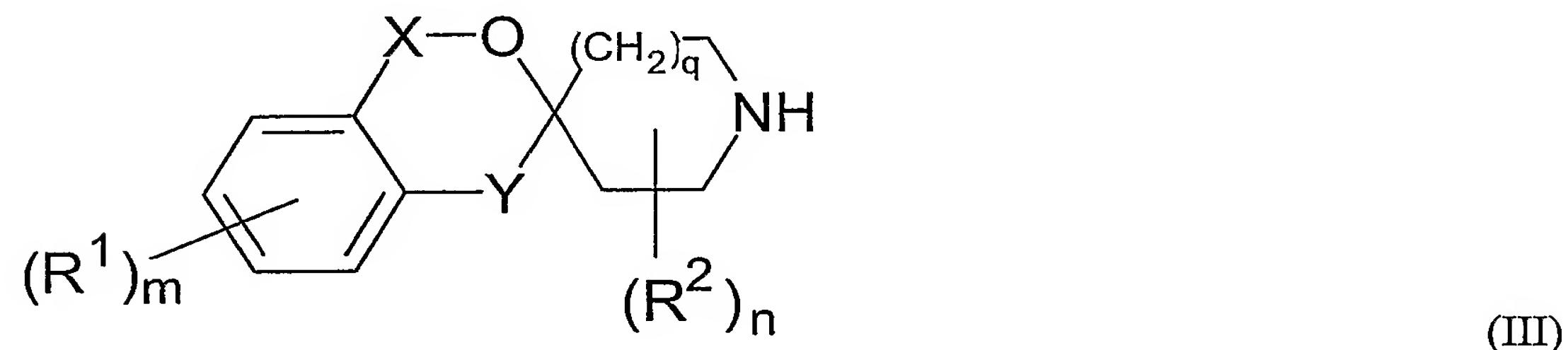
11. A process for the preparation of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or solvate thereof which comprises:

(a) converting a compound of formula (II)

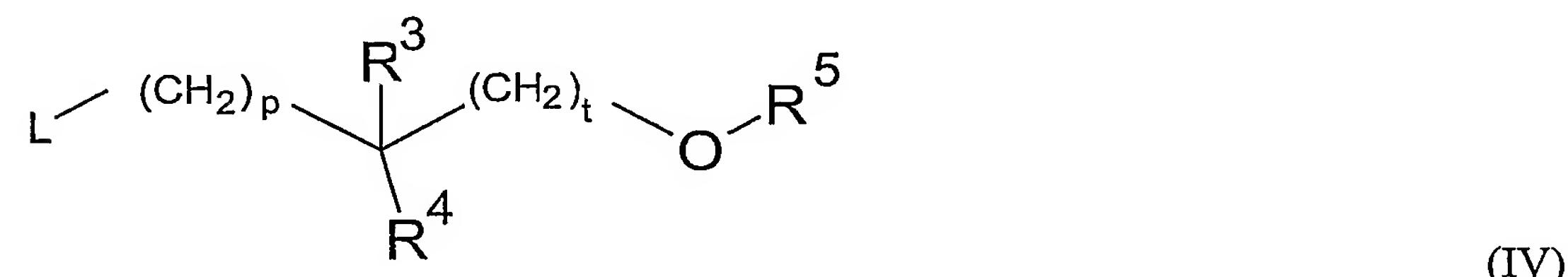


wherein R^1 , m , X , Y , R^2 , n , q , p , R^4 , t and R^5 are as defined in formula (I), into a compound of formula (I); or

10 (b) reacting a compound of formula (III)

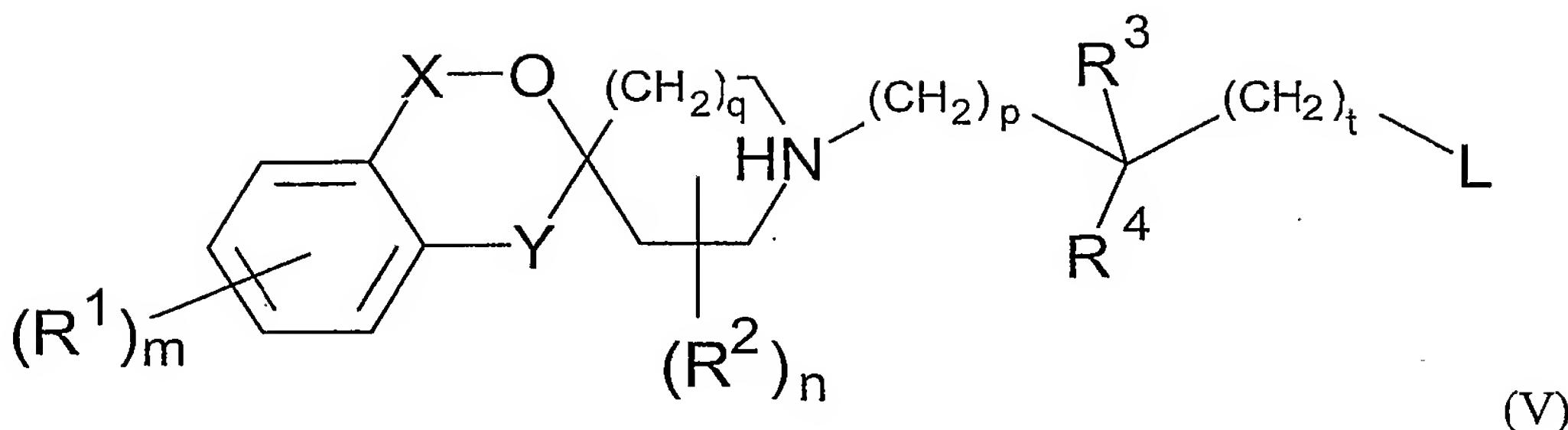


wherein R^1 , m , X , Y , R^2 , n and q are as defined for formula (I), with a compound of 15 formula (IV)



wherein L is a leaving group and p , R^3 , R^4 , t and R^5 are as defined for formula (I);

20 (c) reacting a compound of formula (V)



wherein R^1 , m , X , Y , R^2 , n , q , p , R^3 , R^4 and t are as defined for formula (I), with a compound of formula (VI)



5 wherein L is a leaving group and R^5 is as defined for formula (I);

and optionally thereafter if necessary:

(i) converting a compound of formula (I) into another compound of formula (I);

(ii) removing any protecting groups; or

10 (iii) forming a pharmaceutically acceptable salt or solvate.

12. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 10 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

15

13. A process for the preparation of a pharmaceutical composition as claimed in claim 12 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 10 with a pharmaceutically acceptable adjuvant, diluent or carrier.

20

14. A compound of formula (I) or a pharmaceutically-acceptable salt or solvate thereof as claimed in any one of claims 1 to 10 for use in therapy.

15. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 10 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.

16. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 10 in the manufacture of a medicament for use in treating rheumatoid arthritis.

5

17. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 10 in the manufacture of a medicament for use in treating chronic obstructive pulmonary disease.

10

18. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 10 in the manufacture of a medicament for use in treating asthma.

15

19. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 10 in the manufacture of a medicament for use in treating multiple sclerosis.

20

20. A method of treating an inflammatory disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 10.

25

21. A method of treating an airways disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 10.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2004/001938

A. CLASSIFICATION OF SUBJECT MATTER

C07D471/10, C07D221/20, C07D209/54 A61K31/438,
A61K31/403, A61K31/407, A61P11/06, A61P11/08, A61P19/02, A61P29/00

IPC7: C07D 491/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9825605 A1 (MERCK & CO., INC.), 18 June 1998 (18.06.1998), see particularly examples 30-42 --	1-21
A	WO 0014086 A1 (LEUKOSITE INC.), 16 March 2000 (16.03.2000), see particularly examples 68-77 --	1-21
A	Eur J Med Chem, Vol. 31, 1996, MD Pujol et al: "Novel tricyclic spiropiperidines. Synthesis and adrenergic activity of spiro(1,3-benzodioxolopiperidines) and spiro(1,3-benzodioxanepiperidines)", page 889 - page 894 --	1-21

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

31 March 2005

Date of mailing of the international search report

06-04-2005

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0164213 A1 (SMITHKLINE BEECHAM CORPORATION), 7 Sept 2001 (07.09.2001) --	1-21
A	WO 9831364 A1 (MERCK & CO., INC.), 23 July 1998 (23.07.1998) --	1-21
A	EP 0004951 A1 (HOECHST AKTIENGESELLSCHAFT), 31 October 1979 (31.10.1979) --	1-21
A	WO 02102387 A1 (H. LUNDBECK A/S), 27 December 2002 (27.12.2002) --	1-21
P,A	WO 2004005295 A1 (ASTRAZENECA AB), 15 January 2004 (15.01.2004) -- -----	1-21

INTERNATIONAL SEARCH REPORT

International application No.
SE 2004/001938

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 20, 21

because they relate to subject matter not required to be searched by this Authority, namely:

Claims 20 and 21 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic . . . / . . .

2. Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
SE 2004/001938

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

01/03/2005

PCT/SE 2004/001938

WO	9825605	A1	18/06/1998	AU	737107	B	09/08/2001
				AU	4954297	A	29/05/1998
				AU	5803398	A	03/07/1998
				CA	2271146	A	14/05/1998
				EP	0937244	A	25/08/1999
				GB	9703005	D	00/00/0000
				NZ	335885	A	26/01/2001
				US	6387232	B	14/05/2002
				US	5962462	A	05/10/1999

WO	0014086	A1	16/03/2000	AU	2464999	A	27/03/2000
				CA	2342882	A	16/03/2000
				EP	1109804	A	27/06/2001
				JP	2002524458	T	06/08/2002
				US	6288083	B	11/09/2001
				US	6288084	B	11/09/2001
				US	6503926	B	07/01/2003
				US	20020161005	A	31/10/2002

WO	0164213	A1	07/09/2001	AU	4339401	A	12/09/2001
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WO	9831364	A1	23/07/1998	AU	6133098	A	07/08/1998
				CA	2278309	A	23/07/1998
				EP	1003743	A	31/05/2000
				GB	9707490	D	00/00/0000
				JP	2001508798	T	03/07/2001
				US	6124319	A	26/09/2000

EP	0004951	A1	31/10/1979	CA	1132988	A	05/10/1982
				CA	1132989	A	05/10/1982
				DE	2961804	D	00/00/0000
				ES	479368	A	16/07/1979
				JP	54145660	A	14/11/1979
				US	4166120	A	28/08/1979

WO	02102387	A1	27/12/2002	NONE		
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WO	2004005295	A1	15/01/2004	AU	2002353713	A	00/00/0000
				CA	2462819	A	30/05/2003
				EP	1451356	A	01/09/2004
				SE	0202133	D	00/00/0000
				US	20050003361	A	06/01/2005